Compound Name:	Cimetidine
Compound Type:	Inhibitor
Prefix:	SV
Species:	Human
Simcyp Version this document relates to:	V19
File data last updated:	V13.1 file created V17. Ki values added for CYP3A4 and 2D6 V19. Hepatic OCT1 Ki value added, renal OCT2 and MATE Ki values updated. For this summary: CYP3A4 Ki value updated, CYP1A2 and CYP2C19 Ki values added
Population used in Performance Verification:	Sim-Healthy Volunteer, Sim-Chinese-Healthy Volunteer, Sim-Japanese

Prepared: April 2025

The cimetidine model within the Simcyp Compound Database has been developed primarily as an inhibitor of renal transporters (OCT2 and MATEs). It also includes Ki values for CYP3A4 and CYP2D6.

Note: For this summary the CYP3A4 Ki value is reoptimised with a clinical study using Triazolam as probe (Abernethy *et al.,* 1983). In addition, CYP1A2 and CYP2C19 Ki values were added.

This document provides:

1. Examples of model performance
2. A summary of the key pharmacokinetic features of cimetidine considered within the model

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1. MODEL PERFORMANCE.

SV-Cimetidine Model Summary

Absorption	1st order absorption	User input P_{eff} via Loc-I-Gut experiments; fa and ka optimised from clinical studies
Distribution	Full PBPK model	Predicted V_{ss} using the Rodgers and Rowland method (Method 2)
Elimination	Enzyme Kinetics	Additonal HLM Clearance (via retrograde calculator); Renal clearance via the Mechanistic Kidney model
Transport	Kidney	J_{max} & K_m inputs for OCT2 (SLC22A2); OAT3 (SLC22A8); MATE2-K (SLC47A2) input as MRP4 (ABCC4); MATE1 (SLC47A1) input as MATEs (SLC47As).
Interaction	Competitive inhibition	OCT2 and MATEs in kidney, OCT1 in liver CYP3A4, CYP2D6, CYP2C19, and CYP1A2

Optimised Parameters:

- MATEs Ki
- RAFs for renal transporter
- CYP2D6 Ki

- CYP3A4 Ki
- CYP1A2 Ki
- CYP2C19 Ki

Characteristics:

Drug characteristics based on the DIDB drug monograph DDI summary.

Monographs - Certara Drug Interaction Solutions

- CYP1A2 weak inhibitor
- CYP2C19 weak inhibitor
- CYP2C9 weak inhibitor
- CYP2D6 weak inhibitor
- CYP3A weak inhibitor
- MATE1 FDA clinical inhibitor
- MATE2-K FDA clinical inhibitor
- OCT2 FDA clinical inhibitor
- P-gp clinical inhibitor

INTRAVENOUS ADMINISTRATION

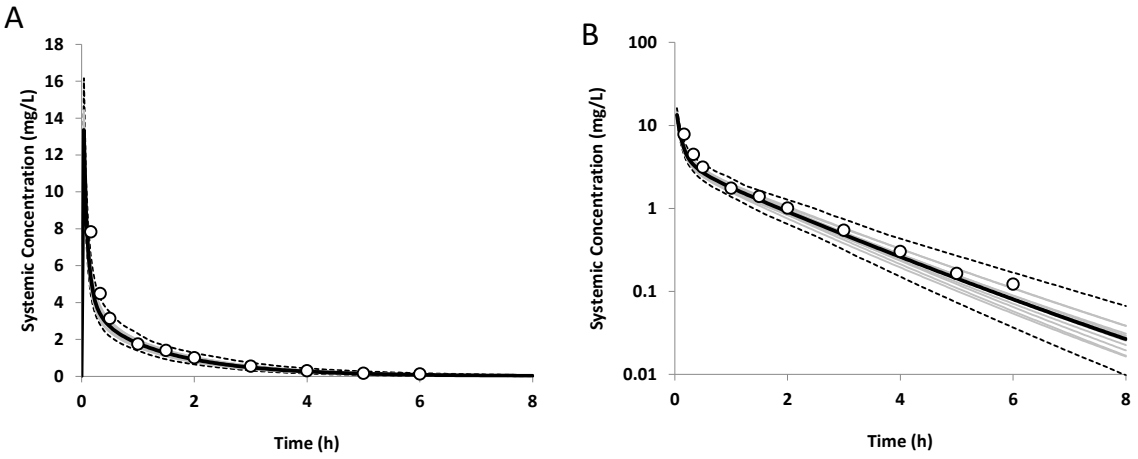

Figure 1. Simulated (black line) and observed (data points) mean plasma concentration-time profiles of cimetidine after a **single iv dose** of 300 mg (10 trials of 8 male subjects, 21-35 years). The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Figure 1B shows the data plotted with the y-axis on a log scale. Observed data were extracted from Lebert *et al.,* 1981. This study formed part of the meta-analysis to back calculate metabolic CL_{int}.

ORAL ADMINISTRATION

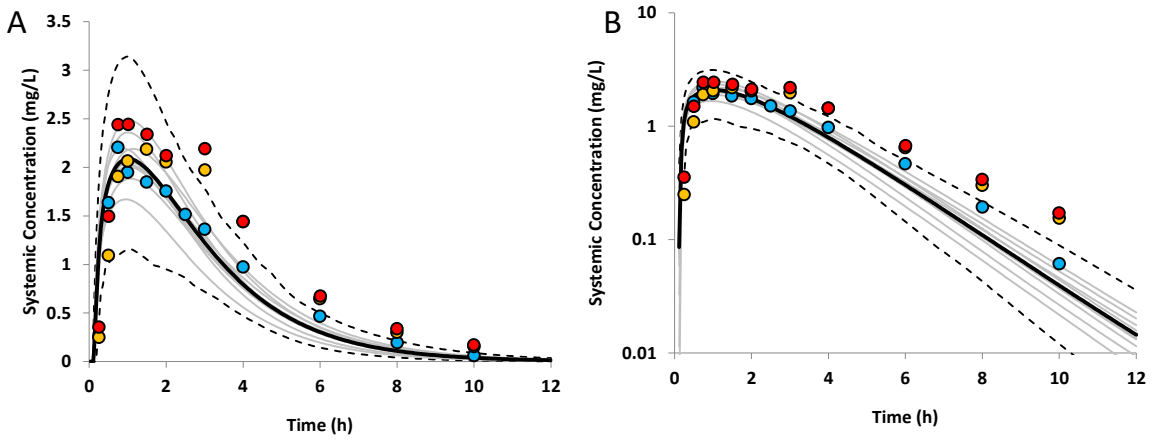

Figure 2. Simulated (black line) and observed (data points) mean plasma concentration-time profiles of cimetidine after a **single oral dose** of 400 mg (10 trials of 8 subjects, 22-35 years, 50% female). The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Observed data were extracted from Somogyi *et al.,* 1981 (red circles), Gugler *et al.,* 1981 (yellow circles) and Grahnen *et al.,* 1979 (mean data from 3 subjects) (blue circles). Figure 2B shows the data plotted with the y-axis on a log scale. These studies were used to derive ka and t_{lag}.

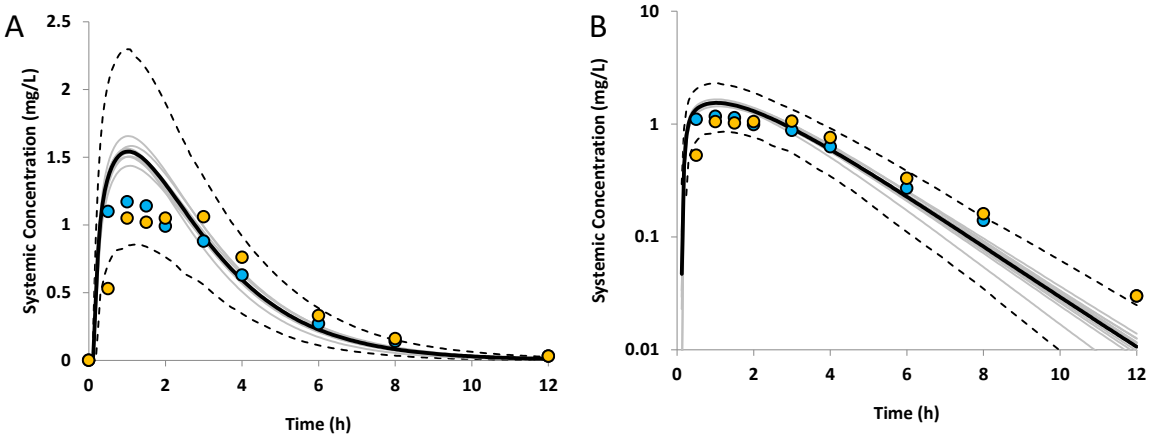

Figure 3. Simulated (black line) and observed (data points) mean **blood** concentration-time profiles of cimetidine after a **single oral dose** of 300 mg (10 trials of 12 subjects, 20-50 years, 50% female). The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Observed data were extracted from Walkenstein *et al.,* 1978 liquid formulation (blue circles), tablet formulation (yellow circles). Figure 3B shows the data plotted with the y-axis on a log scale.

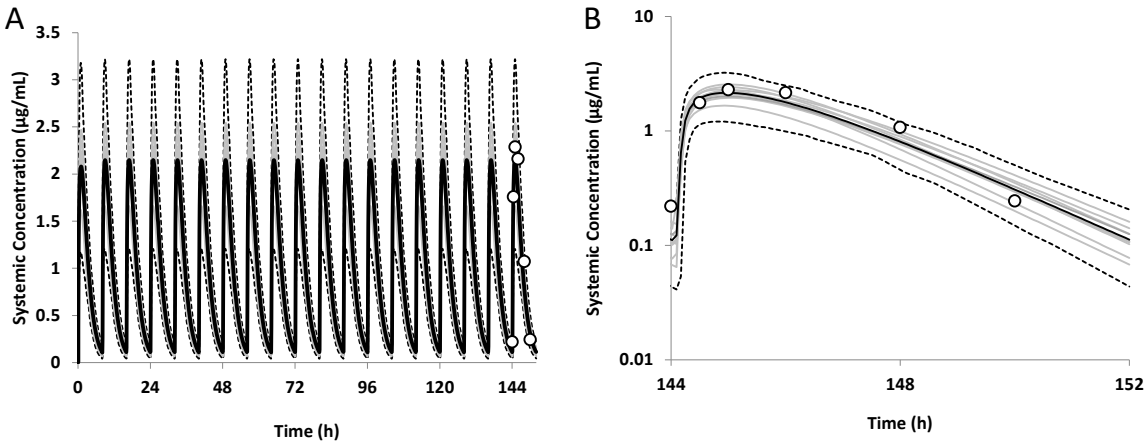

Figure 4. Simulated (black line) and observed (data points) mean plasma concentration-time profile of cimetidine after **multiple oral doses** of cimetidine 400 mg TID (10 trials of 8 subjects, 20-30 years, 40% female). The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Observed data were extracted from Kirch *et al.,* 1989. Figure 4B shows the data from the last dose plotted with the y-axis on a log scale.

2. MODEL OVERVIEW

ABSORPTION

Oral cimetidine is absorbed rapidly and almost completely from the gastrointestinal tract as predicted from Loc-I-gut measurements (Lennernas, 2007) in the simulator using a $P_{eff,man}$ (user input) of 0.26 x 10^{-4} cm/sec. The observed fraction absorbed of 0.92 is based on the fraction excreted in faeces after an oral dose (Taylor *et al.*, 1978), considering the fraction excreted in faeces after an IV dose. Peak plasma concentrations are reached within 2 hours (Gugler *et al.,* 1981 and Somogyi *et al.*, 1981).

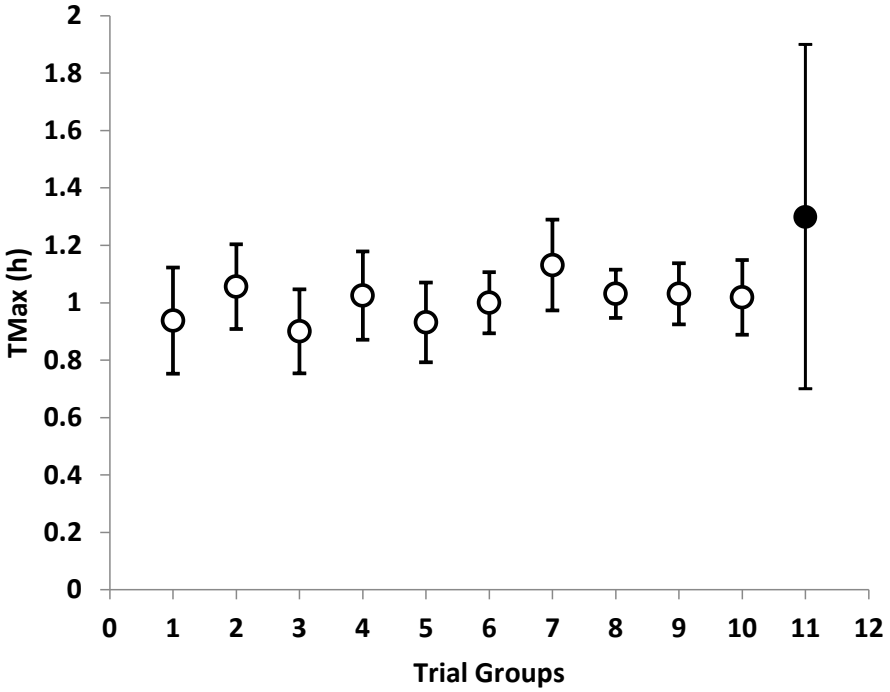

Figure 5. Simulated (○) (10 trials of 8 subjects, 20-30 years, 40% female) and observed (●) mean values of T_{max} (± SD) for the last (19^{th}) dose of cimetidine after **multiple oral doses** of 400 mg TID. Observed data were reported by Kirch *et al.,* 1989.

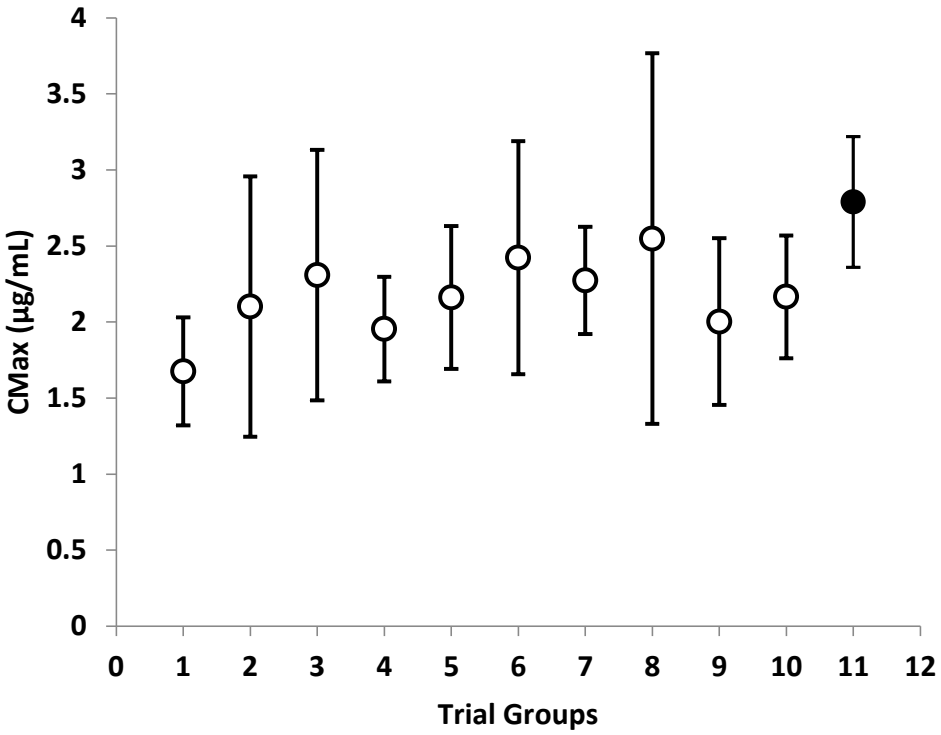

Figure 6. Simulated (○) (10 trials of 8 subjects, 20-30 years, 40% female) and observed (●) mean values of C_{max} (± SD) for the last (19^{th}) dose of cimetidine after **multiple oral doses** of 400 mg TID. Observed data were reported by Kirch *et al.,* 1989.

DISTRIBUTION

A -body distribution model was used for the Cimetidine compound file; the predicted V_{ss} (using Method 2; (Rodgers *et al.,* 2005b; Rodgers *et al.,* 2005a; Rodgers *et al.,* 2006; Rodgers *et al.,* 2007) was Following intravenous administration, cimetidine has a predicted steady state volume of distribution of around approximately 0.55 L/kg (Figure 7). Cimetidine is approximately 20% bound to plasma proteins (Taylor *et al.*, 1978; Somogyi *et al.*, 1980).

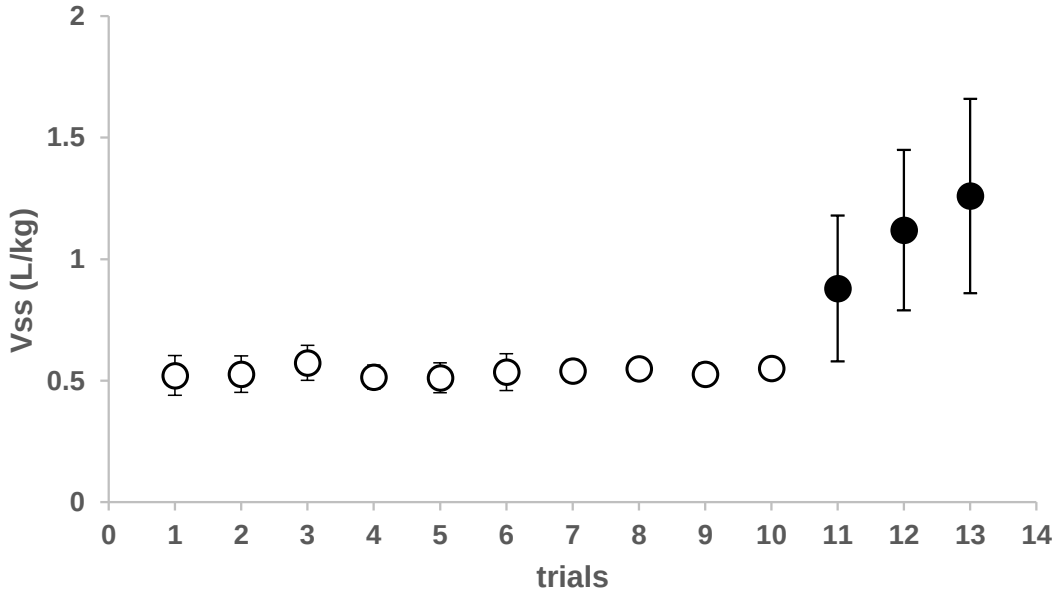

Figure 7. Simulated (○) (10 trials of 10 subjects, 20-35 years 50% female) and observed (●) mean values of SV-Cimetidine V_{ss} (±SD) after a single iv dose of 300 mg. Observed data were obtained from Burgess *et al.,* 1980, Lebert *et al.,* 1981, and Villeneuve *et al.,* 1983.

ELIMINATION

The cimetidine file does not contain any enzyme kinetic inputs for specific enzyme isoforms. However, the enzyme kinetic option is selected so that the necessary transporter components can be incorporated into the file. To capture the entire metabolic clearance component, total and renal clearances were used as inputs into the retrograde calculator. The resulting metabolic CL_{int} was applied as an additional HLM CL_{int} based on retrograde calculations from IV clearance data (Walkenstein *et al.,* 1978; Grahnen *et al.,* 1979; Burgess *et al.,* 1980; Lebert *et al.,* 1981; Villeneuve *et al.,* 1983 and Somogyi *et al.,* 1985) and renal clearance data (Walkenstein *et al.,* 1978; Grahnen *et al.,* 1979; Burgess *et al.,* 1980; Villeneuve *et al.,* 1983 and Somogyi *et al.,* 1985). The cimetidine file uses the mechanistic kidney model (MechKiM) to predict renal clearance.

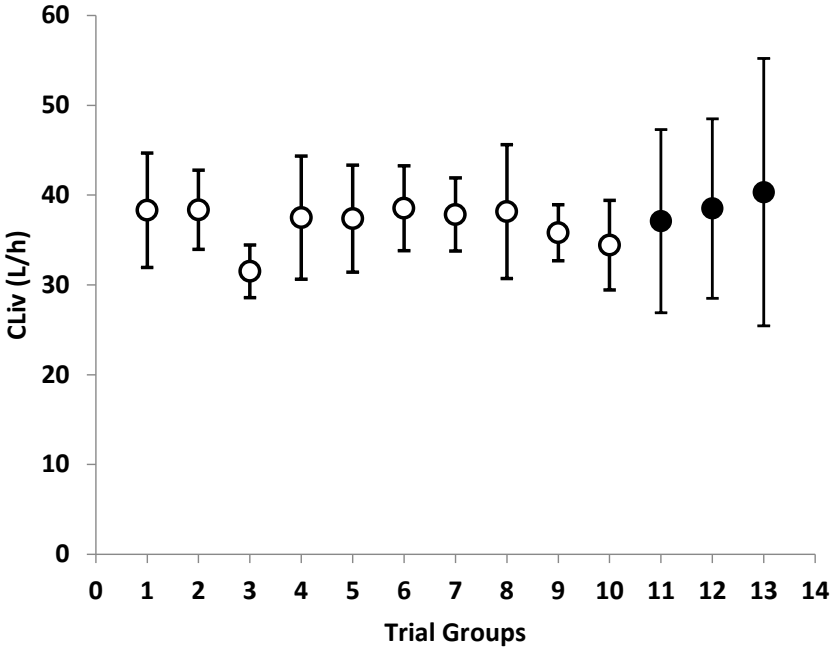

Figure 8. Simulated (○) (10 trials of 10 subjects, 20-35 years 50% female) and observed (●) mean values of CL_{iv} for cimetidine (± SD) after a single iv dose of 300 mg. Observed data are from Burgess *et al.,* 1980, Lebert *et al.,* 1981, and Villeneuve *et al.,* 1983. These studies formed part of the meta analysis to back calculate metabolic CL_{int}.

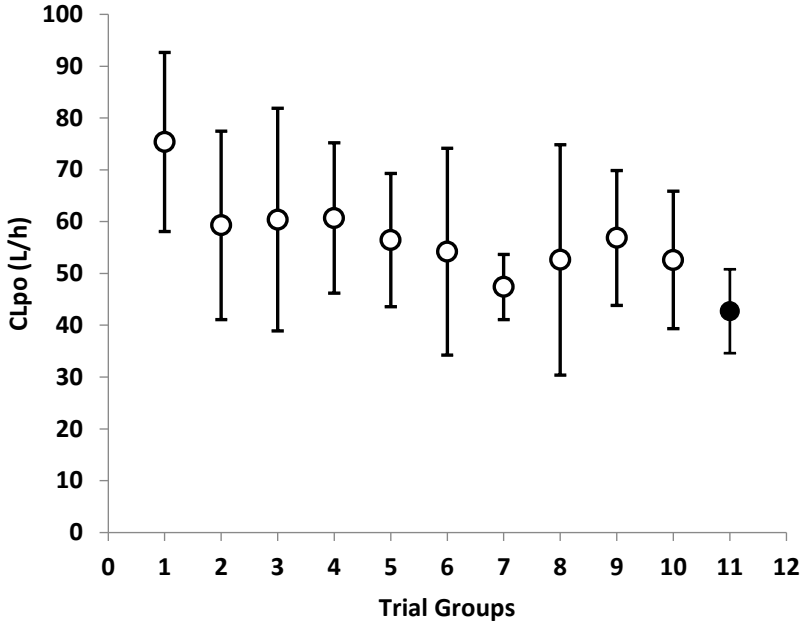

Figure 9. Simulated (○) (10 trials of 8 subjects, 20-30 years, 40% female) and observed (●) mean values of steady state CL_{po} (± SD) after **multiple oral doses** of 400 mg TID. Observed data were reported by Kirch *et al.,* 1989.

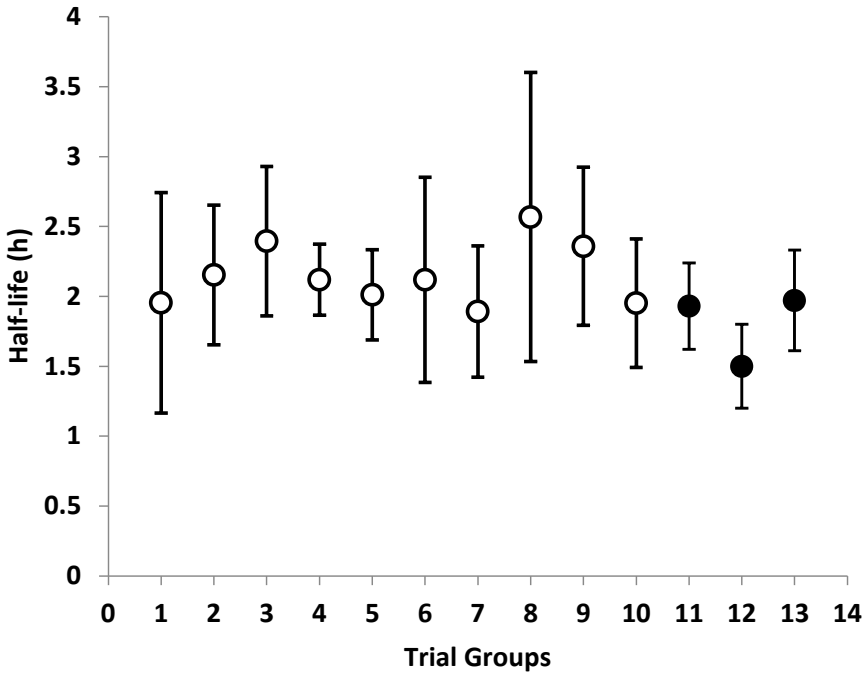

Figure 10. Simulated (○) (10 trials of 8 subjects, 20-35 years 50% female) and observed (●) mean values of cimetidine half life (± SD) after a single oral dose of 400 mg. Observed data were reported by Somogyi *et al.,* 1981, Grahnen *et al.,* 1979, and Gugler *et al.,* 1981.

INTERACTION

A) Transporter

The V19 SV-Cimetidine library file contains competitive Ki values for OCT2 and MATEs in the kidney.

The observed DDI between metformin and cimetidine, an inhibitor of MATE and to a lesser extent OCT transporters has been simulated with the current V19 metformin and cimetidine compound files. The V19 metformin file uses the electrochemical gradient driven (EGD) transport model for OCT2 transport and the cimetidine OCT2 and MATE Ki values have been updated to reflect this.

Data from two studies involving the co-administration of metformin (250 mg QD and 500 mg single dose) and cimetidine (400 mg BID) were also simulated (Somogyi *et al.,* 1987; Wang *et al.*, 2008). For each study, ten trials were simulated in which the number, age range and gender of the virtual subjects were matched to those of the real subjects. The Sim-Healthy Volunteer (HV) population library was used to simulate trials conducted in healthy Caucasian subjects and the Chinese-Healthy Volunteer population library was used to simulate the DDI study of Wang *et al.,* 2008. In the latter study, mean plasma metformin concentrations and PK parameters were reported for different genotypes of the OCT2 808G > T variant. In this case, population mean values were generated using the expected number of individuals with each genotype, based on the allele frequency reported in the study and assuming Hardy–Weinberg equilibrium.

Table 1. Dosing regimen for DDI studies

					Dosage regimen	
Study	**Pop**	**Age range**	**N**	**% female**	**Inhibitor**	**Substrate**
Somogyi *et al.,* 1987	Sim-HV	19–23	7	57	400 mg cimetidine BID for 5 days	250 mg metformin HCl QD for 5 days
Wang *et al.,* 2008	Sim-Chinese-HV	21-32	6	0	400 mg cimetidine BID for 7 days	500 mg metformin HCl SD on day 7

Table 2. Observed and predicted mean ratios of metformin C_{max} and AUC in the presence of cimetidine compared to metformin administered alone. The predicted value represents the mean of the total population (Somogyi *et al.,* 1987: 10 trials x 7 subjects; Wang *et al.,* 2008: 10 trials x 6 subjects) whereas the values in brackets indicate the range of individual trial means.

	Observed		**Predicted**		**Predicted/ Observed**	
Cimetidine DDI	**C_{max} ratio**	**AUC ratio**	**C_{max} ratio**	**AUC ratio**	**C_{max} ratio**	**AUC ratio**
Somogyi *et al.,* 1987	1.73	1.46	1.44 (1.35 – 1.50)	1.45 (1.34 – 1.51)	0.83	0.99
Wang *et al.,* 2008	1.40	1.46	1.31 (1.27 – 1.36)	1.36 (1.31 – 1.42)	0.94	0.93

A) CYP

Competitive inhibition parameters for CYP3A4 and CYP2D6 were added to SV-Cimetidine. The **CYP3A4 Ki** of 11 µM was optimised using the DDI with triazolam reported by Abernethy *et al.,* 1983. The **CYP2D6 Ki** of 3.5 µM was optimised using the DDI with metoprolol reported by Kirch *et al.,* 1984. For the matrix in vitro-derived **Ki values for CYP1A2** (**4.58 µM)** and **CYP2C19** (**8.22 µM)** for **cimetidine** were scaled using an *in vitro/in vivo* optimisation scalar of 43.6. That scalar was originally obtained for the CYP3A4 Ki for cimetidine comparing the average reported *in vitro* Ki values from the Washington database (December 2023) to the *in vivo* relevant Ki for CYP3A4 to recover the DDI between triazolam and cimetidine (Abernethy *et al.,* 1983). Table 3 shows the results of the simulation of the Abernethy *et al.,* 1983 triazolam-cimetidine study using a CYP3A4 Ki of 11 µM

Table 3 Triazolam-cimetidine interaction (Abernethy *et al.,* 1983) with optimised CYP3A4 Ki of 11 µM

	Control		**+ Cimetidine**		**Ratio**	
	C_{max} (ng/mL)	**AUC (ng/mL.h)**	**C_{max} (ng/mL)**	**AUC (ng/mL.h)**	**C_{max}**	**AUC**
Predicted	4.2	26.3	5.6	40.4	1.33	1.54
Observed	4.9	24.5	5.9	37.8	1.20	1.54
Predicted/Observed	0.86	1.07	0.95	1.07	1.11	1.00

CYP3A4 interactions

DDI studies with the CYP3A4 substrates midazolam, triazolam, alprazolam, nifedipine, quinidine, sildenafil, carbamazepine, verapamil, and zolpidem are shown in Tables 4 and 5. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 3. All doses of substrates and cimetidine were given orally. All substrates were default V19 library files. Simulated and observed AUC and C_{max} ratios are shown in Table 5.

Table 4. Dosing regimens for CYP3A4 DDI studies.

	Dosage regimen	
Study	**Inhibitor (Cimetidine)**	**Substrate**
Fee *et al.,* 1987	400 mg BID (3 doses)	Midazolam 15 mg SD (Day 2) (30 min after cimetidine)
Salonen *et al.,* 1986	400 mg SD	Midazolam 15 mg SD (2 hrs after cimetidine)
Elliott *et al.,* 1984	200 mg TID with 400 mg at night on day 1, 200 mg on day 2	Midazolam 15 mg SD (Day 2) (2.5 hr after cimetidine)
Friedman *et al.,* 1988	300 mg QID for 2 days	Triazolam 0.5 mg SD (Day 2)
Pourbaix *et al.,* 1985a	200 mg TID with 400 mg at night for 9 days	Triazolam 0.5 mg QD at night for 7 days
Cox *et al.,* 1986*	300 mg QID (4 doses)	Triazolam 0.5 mg SD (1 hr after 3rd cimetidine dose)
Pourbaix *et al.,* 1985b	200 mg TID with 400 mg at night for 9 days	Alprazolam 0.5 mg TID for 7 days and morning dose on day 8
Khan *et al.,* 1991	800 mg QD for 5 days	Nifedipine 10 mg TID for 4 days, 1 dose day 5
Kirch *et al.,* 1984	200 mg TID with 400 mg at night for 7 days	Nifedipine 10 mg QID for 6 days, 1 dose day 7
Schellens *et al.,* 1989[#]	200 mg TID with 400 mg at night for 3 days	Nifedipine 20 mg SD day 2 (1 hr after first cimetidine dose)
Schwartz *et al.*, 1988	300 mg QID for 7 days	Nifedipine 20 mg SD day 7
Smith *et al.,* 1987	800 mg QD for 5 days	Nifedipine 20 mg SD day 5 (1 hr after cimetidine)
Hardy *et al.,* 1983	300 mg QID for 7 days	Quinidine 330 mg (free base) SD on day 6
Kolb *et al.,* 1984	300 mg QID for 3 days, morning dose day 4	Quinidine 330 mg (free base) SD on day 4
Wilner *et al.,* 2002	800 mg QD for 4 days	Sildenafil 50 mg SD day 3 (2 hrs after cimetidine)
Martinez *et al.,* 1999	800 mg SD	Midazolam 7.5 mg SD
Abernethy *et al.,* 1983	300 mg QID (14 doses)	Alprazolam 1 mg on day 2
Renwick *et al.,* 1987	400 mg TID for 4 doses	Nifedepine 10 mg on day 2
Dalton *et al.,* 1985	300 mg QID for 9 days	Carbamazepine 600 mg on day 3
Smith *et al.,* 1984	300 mg QID for 9 days	Verapamil 120 mg on day 8
NDA_019908	200 mg TID and 400 mg at night on day 1; 200 mg on day 2	Zolpidem 16.08 mg on day 2

[#]Cocktail study;

*Triazolam was infused directly into the duodenum, by-passing the stomach and gastric emptying.

Table 5. Observed and predicted mean C_{max} and AUC ratios for cimetidine interactions with CYP3A4 substrates. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design.

	Observed		Predicted		Predicted/ Observed	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Fee *et al.,* 1987	ND	1.35	1.57 (1.50-1.63)	1.74 (1.64-1.85)	ND	1.29
Salonen *et al.,* 1986	1.37	1.36	1.42 (1.34-1.52)	1.51 (1.41-1.65)	1.04	1.11
Elliott *et al.,* 1984	2.38	2.02	1.19 (1.13-1.23)	1.22 (1.15-1.27)	0.50	0.60
Friedman *et al.,* 1988	1.39	1.32	1.36 (1.27-1.42)	1.55 (1.45-1.64)	0.98	1.17
Pourbaix *et al.,* 1985a	1.51	2.20	1.41 (1.33-1.46)	1.57 (1.44-1.64)	0.93	0.71
Cox *et al.,* 1986*	1.35	1.55	1.30 (1.19-1.39)	1.42 (1.30-1.53)	0.96	0.92
Pourbaix *et al.,* 1985b	1.82	1.73	1.13 (1.11-1.15)	1.31 (1.26-1.35)	0.62	0.76
Khan *et al.,* 1991**	2.3	2.01	1.52 (1.41-1.63)	2.00 (1.87-2.15)	0.66	1.00
Kirch *et al.,* 1984	2.02	1.60	1.26 (1.21-1.32)	1.50 (1.40-1.59)	0.62	0.94
Schellens et al., 1989[#]	ND	1.31	1.32 (1.27–1.38)	1.48 (1.41-1.54)	ND	1.13
Schwartz *et al.*, 1988	1.60	1.80	1.39 (1.34-1.42)	1.66 (1.59-1.71)	0.87	0.92
Smith *et al.,* 1987	1.65	1.77	1.88 (1.78-2.04)	2.32 (2.15-2.58)	1.14	1.31
Hardy *et al.,* 1983~	1.2	1.57	1.12 (1.09-1.15)	1.30 (1.25-1.37)	0.93	0.83
Kolb *et al.,* 1984~	0.99	1.27	1.11 (1.09-1.13)	1.17 (1.15-1.21)	1.12	0.92
Wilner *et al.,* 2002~	1.35	1.41	1.63 (1.56-1.75)	1.77 (1.67-1.89)	1.21	1.26
Martinez *et al.,* 1999	ND	1.5	1.63 (1.55-1.74)	2.00 (1.86-2.15)	ND	1.33
Abernethy *et al.,* 1983	1.03	1.58	1.03 (1.02-1.04)	1.23 (1.19-1.27)	1.00	0.78
Renwick *et al.,* 1987	1.84	1.84	1.43 (1.35-1.52)	1.70 (1.60-1.87)	0.77	0.92
Dalton *et al.,* 1985	ND	1.25	1.04 (1.03-1.05)	1.21 (1.19-1.24)	ND	0.97
Smith *et al.,* 1984	1.13	1.37	1.35 (1.28-1.41)	1.35 (1.28-1.42)	1.19	0.98
NDA_019908~	1.1	1.3	1.09 (1.07-1.11)	1.19 (1.14-1.25)	0.99	0.91

**Simulated as fed study. Although fasted overnight, a light breakfast is given in the morning.
*Triazolam was infused directly into the duodenum, by-passing the stomach and gastric emptying.
[#]Cocktail study
~An additional weak CYP2C9 inhibition by Cimetidine is currently not considered. Quinidine, Sildenafil, and Zidovudine have a fm_{CYP2C9} of approximately 1%, <10%, and <3%, respectively.
ND – not determined

CYP2D6 interactions

DDI studies with the CYP2D6 substrates metoprolol, desipramine, imipramine, paroxetine, nebivolol, and propranolol are shown in Tables 6 and 7. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 6. All doses of substrates and cimetidine were given orally. All substrates were default V19 library files. Nebivolol and propranolol were research files (compound summary available). Simulated and observed AUC and C_{max} ratios are shown in Table 7.

Table 6. Dosing regimens for CYP2D6 DDI studies

	Dosage regimen	
Study	**Inhibitor (Cimetidine)**	**Substrate**
Kirch *et al.,* 1982	200 mg TID with 400 mg at night for 7 days	Metoprolol tartrate 100 mg BID for 7 days (13 doses)
Mutschler *et al.,* 1984	200 mg TID with 400 mg at night for 7 days	Metoprolol tartrate 100 mg BID for 7 days (13 doses)
Chellingsworth *et al.,* 1988	800 mg QD for 8 days	Metoprolol tartrate 100 mg SD day 8
Chellingsworth *et al.,* 1988	800 mg QD for 8 days	Metoprolol tartrate 100 mg BID for 8 days (15 doses)
Steiner *et al.,* 1987 CYP2D6 EMs	400 mg TID for 9 days	Desipramine 25 mg SD day 6
Abernethy *et al.,* 1984	400 mg QID (5 days)	Imipramine 44.25 mg (free base) SD (12 hrs after 1st cimetidine dose)
Henauer and Hollister 1984	300 mg QID for 2 days, single 300 mg dose day 3	Imipramine 88.5 mg (free base) SD day 3
Wells *et al.,* 1986	300 mg QID for 6 days	Imipramine 88.5 mg (free base) SD day 4
Greb *et al.,* 1989	200 mg QID for 8 days	Paroxetine 30 mg on day 8
Bannister *et al.,* 1989	300 mg TID from day 22 to 28	Paroxetine 30 mg MD for 28 days
Kamali *et al.,* 1997	300 mg BID 24h before and 48 h after nebivolol administration	Nebivolol 5 mg (4.59 free base) SD day 2
Tateishi *et al.,* 1992	400 mg TID (10 doses)	Propranolol 20 mg SD
Kirch *et al.,* 1982	200 mg TID 7 days	Propranolol 80 mg BID 7 days
Duchin *et al.,* 1984	300 mg QID 2 days before and on the day	Propranolol 80 mg SD

Table 7. Observed and predicted mean C_{max} and AUC ratios for cimetidine interactions with CYP2D6 substrates. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design

	Observed		Predicted		Predicted/ Observed	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Kirch *et al.,* 1982 Metoprolol	1.60	1.62	1.53 (1.44-1.64)	1.77 (1.63-1.98)	0.96	1.09
Mutschler *et al.,* 1984 Metoprolol	1.60	1.62	1.53 (1.39-1.64)	1.89 (1.68-2.08)	0.96	1.17
Chellingsworth *et al.,* 1988 Metoprolol**	1.63	1.62	1.89 (1.69-2.04)	2.16 (1.86-2.42)	1.16	1.33
Chellingsworth *et al.,* 1988 Metoprolol**	1.51	1.56	1.85 (1.70-1.98)	2.08 (1.88-2.30)	1.23	1.33
Steiner *et al.,* 1987 CYP2D6 EMs Desipramine	ND	1.57	1.55 (1.37-1.75)	1.91 (1.68-2.08)	ND	1.22
Abernethy *et al.,* 1984 Imipramine	1.78	1.86	1.28 (1.20-1.40)	1.40 (1.31-1.51)	0.72	0.75
Henauer and Hollister 1984 Imipramine	0.90	1.40	1.26 (1.18-1.37)	1.23 (1.17-1.31)	1.40	0.88
Wells *et al.,* 1986 Imipramine	1.65	2.72	1.27 (1.20-1.33)	1.39 (1.29-1.50)	0.77	0.51
Greb *et al.,* 1989 Paroxetine**	1.01	1.17	1.64 (1.43-1.85)	2.07 (1.64-2.43)	1.62	1.77
Bannister *et al.,* 1989 Paroxetine**	1.45	1.51	1.27 (1.14-1.41)	1.32 (1.16-1.47)	0.88	0.87
Kamali *et al.,* 1997 Nebivolol	1.23	1.48	2.27 (2.06-2.45)	2.11 (1.99-2.26)	1.84	1.42
Tateishi *et al.,* 1992 Propranolol[#]	2.02	1.89	2.01 (1.74-2.44)	2.06 (1.79-2.49)	1.00	1.09
Kirch *et al.,* 1982 Propranolol	1.99	1.91	1.70 (1.54-1.87)	1.73 (1.58-1.90)	0.85	0.91
Duchin *et al.,* 1984 Propranolol	1.35	1.46	1.85 (1.71-1.97)	2.02 (1.87-2.17)	1.37	1.38

ND – not determined

** GeoMean

[#]The Sim-Japanese population was used.

CYP1A2 interactions

DDI studies with the CYP1A2 substrates caffeine and theophylline are shown in Tables 8 and 9. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 8. All doses of substrates and cimetidine were given orally. All substrates were default V19 library files. Simulated and observed AUC ratios are shown in Table 9.

Table 8. Dosing regimens for CYP1A2 DDI studies

	Dosage regimen	
Study	**Substrate**	**Inhibitor (Cimetidine)**
Broughton *et al.,* 1981	Caffeine 300 mg on Day 6	200 mg TID and 400 mg at night for 6 days
May *et al.,* 1982	Caffeine 2 mg/kg on Day 4	300 mg QID for 4 days
Lin *et al.,* 1987	Theophylline 5 mg/kg (IV) on Day 7 (Day 4 in simulation)	300 mg QID for 6 days
Roberts *et al.,* 1981[#]	Theophylline 3 mg/kg (IV) on Day 7 (Day 4 in simulation)	200 mg TID and 400 mg at night for 10 days
Jackson *et al.,* 1981[#]	Theophylline 6 mg/kg (20 min IV infusion) on Day 3	300 mg QID for 2.75 days
Powell *et al.,* 1984[#]	Theophylline 6 mg/kg (30 min IV infusion) on Day 4	300 mg QID for 5 days
Breen *et al.,* 1982	Theophylline 3 mg/kg (30 min IV infusion) on Day 6	200 mg TID and 400 mg at night for 7 days
Jennings *et al.,* 1993[#]	Theophylline 6 mg/kg (20 min IV infusion) on Day 8	300 mg QID for 10 days
Loi *et al.,* 1993	Theophylline 5 mg/kg (30 minutes IV infusion) on Day 5 @7 AM	400 mg BID for 7 days (Day 1 @7 AM to Day 7 @7 PM) (14 doses)
Naline *et al.,* 1988	Theophylline 250 mg oral on Day 7 @8 AM	400 mg BID for 8 days (16 doses)
Reitberg *et al.,* 1981	Theophylline 4 mg/kg oral on Day 8	300 mg QID for 8 days
Lalonde *et al.,* 1983	Theophylline 200 mg oral every 6 hours for 10 days	300 mg QID for 7 days starting on Day 4
Cusack *et al.,* 1985	Theophylline 170 mg oral every 8 hours for 14 days	400 mg TID for 7 days starting on Day 8
Vestal *et al.,* 1987	Theophylline 170 mg oral every 8 hours for 14 days	400 mg TID for 7 days starting on Day 8
Ohashi *et al.,* 1993	Theophylline 200 mg oral on day 3, 1 hour after cimetidine	400 mg TID for 3 days

[#] Aminophylline was administered

Table 9. Observed and predicted mean AUC ratios* for cimetidine interactions with CYP1A2 substrates. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design.

	Observed	Simulated	Simulated/Observed
	AUC ratio	**AUC ratio**	**AUC ratio**
Broughton *et al.,* 1981#	1.38	1.58 (1.46-1.72)	1.14
May *et al.,* 1982#	1.73	1.64 (1.53-1.74)	0.95
Lin *et al.,* 1987**, #	1.41	1.44 (1.36-1.53)	1.02
Roberts *et al.,* 1981	1.41	1.42 (1.34-1.54)	1.01
Jackson *et al.,* 1981**, #	1.67	1.29 (1.18-1.41)	0.77
Powell *et al.,* 1984#	1.56	1.47 (1.43-1.57)	0.94
Breen *et al.,* 1982**,#	1.54	1.37 (1.30-1.50)	0.89
Jennings *et al.,* 1993#	1.36	1.44 (1.38-1.49)	1.06
Loi *et al.,* 1993 – male#	1.34	1.29 (1.21-1.36)	0.96
Naline *et al.,* 1988#	1.64	1.30 (1.21-1.39)	0.79
Reitberg *et al.,* 1981#	1.46	1.37 (1.24-1.47)	0.94
Lalonde *et al.,* 1983#	1.39	1.53 (1.40-1.60)	1.10
Cusack *et al.,* 1985#	1.47	1.46 (1.35-1.55)	0.99
Vestal *et al.,* 1987#	1.41	1.46 (1.37-1.55)	1.04
Ohashi *et al.,* 1993	1.36	1.22 (1.16-1.27)	0.90

*No C_{max} ratios have been reported in the literature for any of the above listed DDIs.
** GeoMean; # AUC calculated from reported clearance data.

CYP2C19 interactions

DDI studies with the CYP2C19 substrates omeprazole (default V19 library file) and voriconazole (compound summary available) are shown in Tables 10 and 11. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 10. All doses of substrates and cimetidine were given orally. Simulated and observed AUC and C_{max} ratios are shown in Table 11.

Table 10. Dosing regimens for CYP2C19 DDI studies

	Dosage regimen	
Study	**Substrate**	**Inhibitor (Cimetidine)**
Miura *et al.,* 2021	Omeprazole 20 mg on Day 6	400 mg BID for 6 days
Purkins *et al.,* 2003	Voriconazole 200 mg BID (13 doses)	400 mg BID (13 doses)

Table 11. Observed and predicted mean C_{max} and AUC ratios for cimetidine interactions with CYP2C19 substrates. Predicted values show mean and trial range from 10 simulated trials matching the clinical study design

	Observed		**Simulated**		**Simulated/ Observed**	
	C_{max} ratio	**AUC ratio**	**C_{max} ratio**	**AUC ratio**	**C_{max} ratio**	**AUC ratio**
Miura *et al.,* 2021 Omeprazole	ND	1.82	ND	1.79 (1.69-1.87)	ND	0.98
Purkins *et al.,* 2003**,# Voriconazole	1.18	1.23	1.16 (1.13-1.18)	1.20 (1.17-1.23)	1.01	0.98

ND – not determined
** GeoMean
# An additional weak CYP2C9 inhibition by Cimetidine is currently not considered. Voriconazole has a fm_{CYP2C9} of <1%.

Table 12. Input parameters for SV-Cimetidine

Parameter	Value	Method/Reference
Molecular weight (g/mol)	252.34	http://www.chemicalize.org
log P	0.48	Avdeef and Berger 2001
Compound type	Monoprotic Base	http://www.chemicalize.org
pKa	6.9	Durant *et al.,* 1977; Avdeef and Berger 2001
B/P	0.97	Somogyi *et al.,* 1980
fu	0.8	Taylor *et al.,* 1978; Somogyi *et al.,* 1980
Main plasma binding protein	Human serum albumin	Wilson *et al.,* 1990
fa	0.92	Taylor *et al.,* 1978
ka (1/h)	0.7	Fitted from Somogyi *et al.,* 1981; Gugler *et al.,* 1981; Grahnen *et al.,* 1979
Lag time (h)	0.15	As above
fu_{gut}	1	
Q_{gut} (L/h)	2.099	Predicted (Yang *et al.* 2007)
Distribution Model	Full PBPK Model	
V_{SS} (L/kg)	0.589	Predicted - Method 2 (Rodgers *et al.,* 2005b; Rodgers *et al.,* 2005a; Rodgers *et al.,* 2006; Rodgers *et al.,* 2007)
CL_{int} (HLM) (µL/min/mg protein)	2.87	Back calculated from meta analyses of CLiv and CL_R. (6 studies inc Walkenstein *et al.,* 1978 and Villeneuve *et al.,* 1983)
Mechanistic Kidney Model		
$CL_{PD,basal}$ (mL/min/million proximal tubular cells)	2.61E-05	Balimane and Chong, 2008
$CL_{PD,apical}$ (mL/min/million proximal tubular cells)	2.61E-05	Balimane and Chong, 2008
$fu_{Kidney,cell}$	1	
fu_{Urine}	1	
Transporter	SLC22A2 (OCT2)	
Function	EGD model	
J_{max}-OCT2 (pmol/min/millivolt/million cells)	2170	Tahara *et al.,* 2005

K_m (µM)	72.6	Tahara *et al.,* 2005
RAF/REF	3	Optimised to recover CLiv and CL_R
Transporter	SLC22A8 (OAT3)	
Function	Uptake	
J_{max} (pmol/min/million cells)	1232	Erdman *et al.,* 2006; Tahara *et al.,* 2005
K_m (µM)	161.5	Erdman *et al.,* 2006; Tahara *et al.,* 2005
RAF/REF	3	Optimised to recover CLiv and CL_R
Transporter	ABCC4 (MRP4)	(surrogate for MATE2-K)
Function	Efflux	
J_{max} (pmol/min/million cells)	216	Ohta *et al.,* 2009
K_m (µM)	18.2	Ohta *et al.,* 2009
RAF/REF	3	Optimised to recover CLiv and CL_R
Transporter	SLC47As (MATEs)	
Function	Efflux	
J_{max} (pmol/min/million cells)	135.5	Matsumoto *et al.,* 2008; Ohta *et al.,* 2009
K_m (µM)	7.7	Matsumoto *et al.,* 2008; Ohta *et al.,* 2009
RAF/REF	3	Optimised to recover CLiv and CL_R
Interaction parameter		
Enzyme	CYP2D6	
Ki (µM)	3.5	Optimised: Kirch *et al.,* 1984
Enzyme	CYP3A4	
Ki (µM)	11	Optimised: Abernethy *et al.,* 1983, Triazolam arm
Enzyme	CYP1A2	
K_i (µM)	4.58	Scaled down using an *in vitro*-to-*in vivo* scalar of 43.6 obtained for CYP3A4 within the same study (Martinez *et al.,* 1999).
Enzyme	CYP2C19	Scaled down using an *in vitro*-to-*in vivo* scalar of 19.2 obtained for an average measured *in vitro* Ki for CYP3A4 (n=12) and the *in vivo* Ki for CYP3A4 of 11 µM.
K_i (µM)	8.22	
Transporter	SLC22A1 (OCT1)	
Organ	Liver	
Ki (µM)	104	Ito *et al.,* 2012
Transporter	SLC22A2 (OCT2)	
Organ	Kidney	
Ki (µM)	124	Ito *et al.,* 2012

Transporter	SLC47As (MATEs)	
Organ	Kidney	
Ki (µM)	0.407	Optimised. 3-fold reduction from lowest in vitro value Ito *et al.,* 2012

WHAT IS NOT CURRENTLY CONSIDERED IN THE MODEL:

- CYP2C9 weak competitive inhibition.
- P-gp comptetitiv inhibition. None of the substrates used in this summary are identified as P-gp substrates in the Washington database.
- The ability to model formulation effects
- The ability to model the pharmacodynamics of cimetidine and it's metabolites

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