Compound Name: Fluvoxamine

Property	Value
Compound type:	Inhibitor
Prefix:	SV
Species:	Human
File data last updated:	V9: permeability data added. V10: SV-file created (ka optimised, V_{ss} optimised, oral CL refined, CL_R optimised, hepatic uptake added, CYP1A2 Ki optimised) V16: Oral CL and hepatic uptake refined. CYP Ki values optimised. V19: V_{max} and Km elimination parameters incorporated to capture non-linear kinetics. Dose updated and dose for free base considered.
Performance Verification Population:	Sim-Healthy Volunteer, Sim-Japanese

Simcyp Version this document relates to: V19R1

Prepared: March 2025

The SV-Fluvoxamine model within the Simcyp Compound Database has been developed primarily as an inhibitor of CYP1A2 but also includes the inhibition of CYP2C19, CYP2C9, CYP3A, and CYP2D6 enzymes.

This document provides:

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

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Model Performance

SV-Fluvoxamine Model Summary

Parameter	Model	Input
Absorption	First-order absorption	User input fa and ka
Distribution	Minimal PBPK model with SAC	Optimised: Q and V_{sac}, User input V_{ss}
Elimination	Enzyme Kinetics	Recombinant CYP2D6 V_{max} and $K_{m,}$ Additional HLM clearance
Interaction	Competitive Inhibition	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 K_I values

File Refinements for V19

Fluvoxamine is dosed clinically as a maleate salt (100 mg maleate salt = 73.3 mg free base). The free base molecular weight is used for dosing. In V19, CYP2D6 V_{max} and Km elimination parameters were incorporated to capture non-linear kinetics. Distribution parameters were also updated. As most of the DDI studies consider multiple dosing regimens, optimisation focused on recovering the multiple dose profiles.

Optimised Parameters

ka, V_{ss}, V_{sac} and Q, CYP2D6 V_{max}, Additional HLM CL, Hepatic uptake, CL_R, CYP Ki values

Drug characteristics based on the DIDB drug monograph DDI summary

Monographs - Certara Drug Interaction Solutions

- CYP1A2 FDA clinical strong index inhibitor
- CYP1A2 strong inhibitor
- CYP2C19 FDA clinical strong index inhibitor
- CYP2C19 strong inhibitor
- CYP2C8 weak inhibitor
- CYP2C9 weak inhibitor
- CYP2D6 moderate sensitive substrate
- CYP2D6 PGx (FDA label) substrate
- CYP2D6 weak inhibitor
- CYP3A weak inhibitor
- P-gp clinical inhibitor

Oral Administration Profiles

Single dose concentration-time profiles

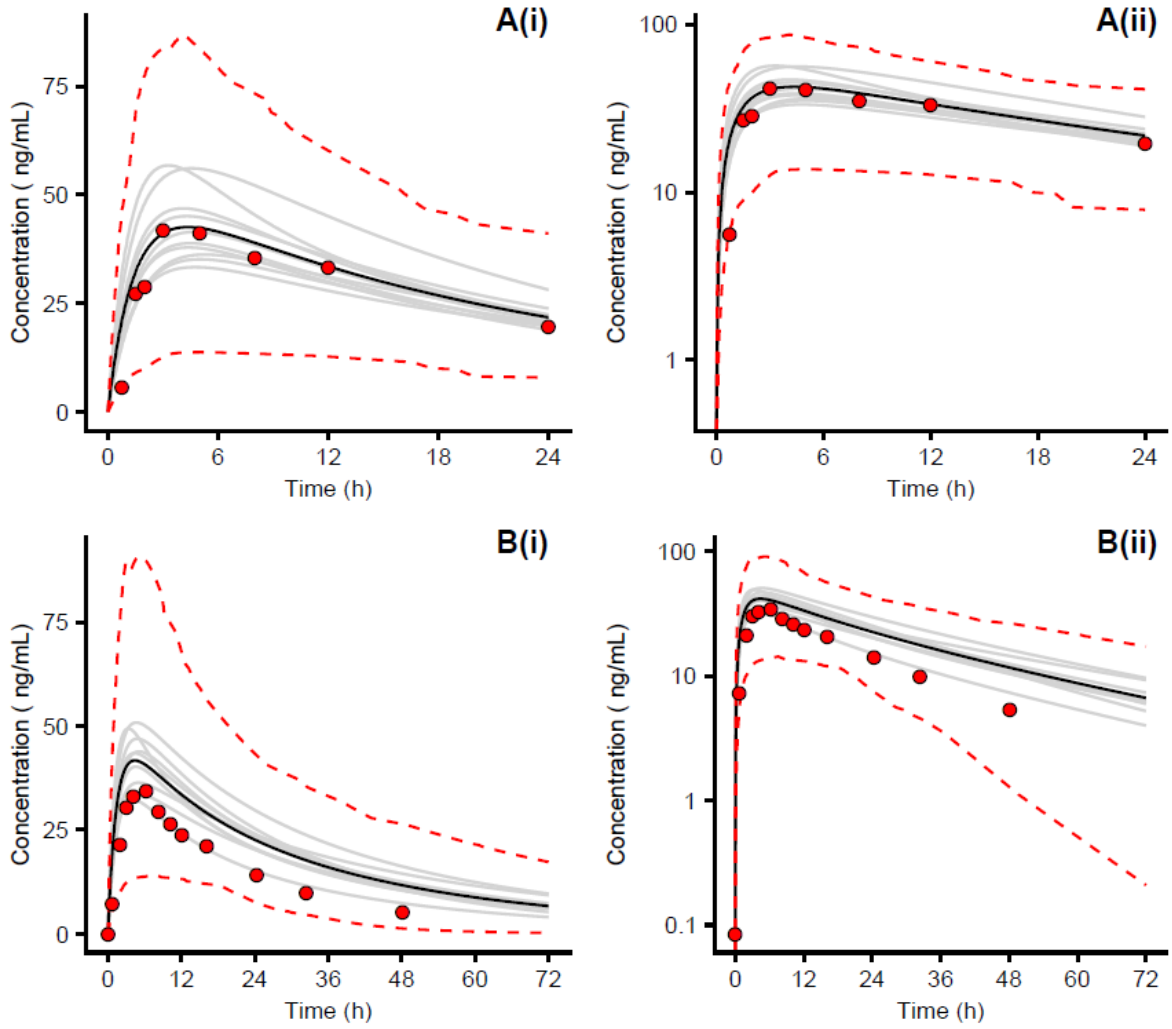

Figure 1: Simulated (black line) and observed (data points) mean plasma concentration-time profiles of fluvoxamine after a single oral dose of 100 mg of fluvoxamine maleate (73.3 mg free base). (A) Ten trials of 10 subjects (10% female), 20-25 years were simulated. Observed data were extracted from De Bree *et al.,* 1983. (B) Ten trials of 12 male subjects, 22-41 years were simulated. Observed data were extracted from De Vries *et al.,* 1993. The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Figures A(ii) and B(ii) show the data plotted with the y-axis on a log scale.

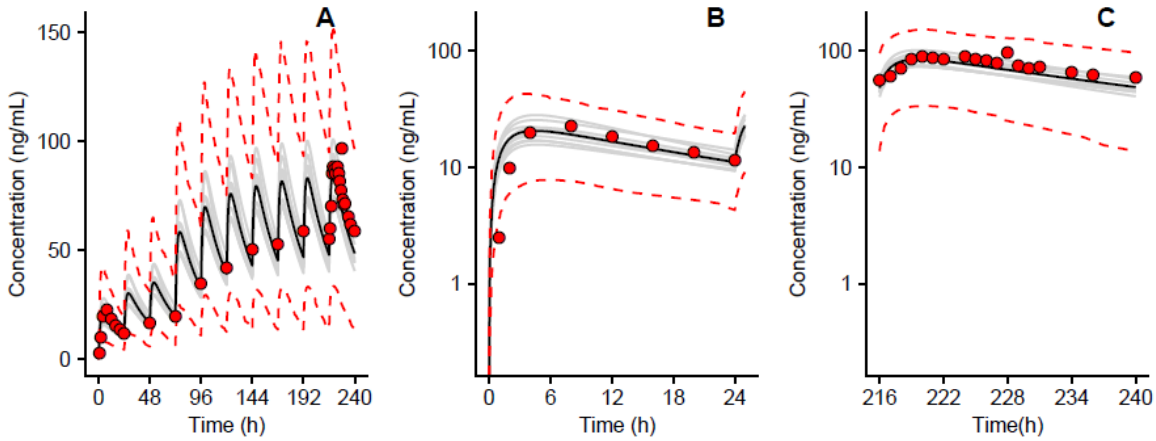

Figure 2: Simulated (black line) and observed (data points) mean plasma concentration-time profiles after multiple oral doses of 50 mg fluvoxamine maleate (36.7 mg free base) QD, days 1-3 and 100 mg (73.3 mg free base) QD days 4-10. Ten trials of 20 male subjects, 20-44 years, were simulated. Observed data were extracted from Fleishaker and Hulst, 1994. The grey lines represent the predictions from individual trials. Dashed lines represent the 5th and 95th percentile of the total virtual population. Figs. 2 B and C show the first and last dose with the y-axis plotted on a log scale.

Model Overview

Absorption

Fluvoxamine undergoes extensive absorption after oral administration of 100 mg fluvoxamine maleate (73.3 mg free base) with a C_{max} of 51.7 ± 16.9 ng/ml and reported T_{max} values between 2-8 h (De Bree *et al.* 1983). Food did not affect T_{max} or C_{max} after administration of 50 mg fluvoxamine maleate (36.7 mg free base) in an immediate release hydroxypropyl-methylcellulose (HPMC) capsule, developed to mask the bitter taste of the drug (van Harten *et al.,* 1991). Reported ka values range between 0.19 and 0.92 h^{-1} (e.g., De Vries *et al.,* 1992). A ka value of 0.7 h^{-1} was optimised to recover observed C_{max} and T_{max} values (Spigset *et al.,* 1998, Culm-Merdeck *et al.,* 2005); these values were then verified using an independent clinical study (De Bree *et al.*, 1983) (Figures 3 and 4, respectively).

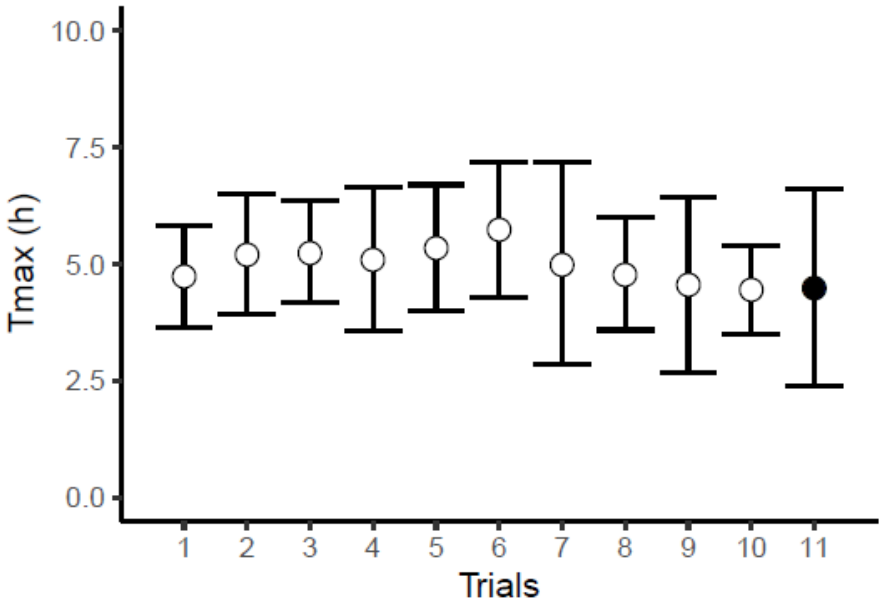

Figure 3: Simulated (◦; 10 trials of 10 subjects; 20-25 years; 10% female, fasted state) and observed (•) mean values of T_{max} (± SD) for fluvoxamine after a single oral dose of 100 mg fluvoxamine maleate (73.3 mg free base) in a hard gelatin capsule (subjects fasted overnight but were allowed a light breakfast 30 minutes after the administration of fluvoxamine). Observed data were reported by De Bree *et al.*, 1983.

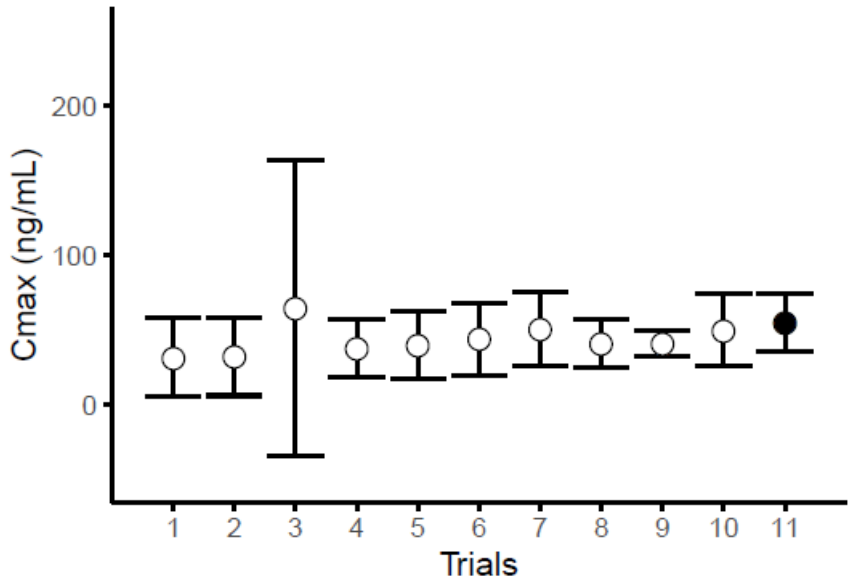

Figure 4: Simulated (◦; 10 trials of 10 subjects; 20-25 years; 10% female) and observed (•) mean values of C_{max} (± SD) for fluvoxamine after a single oral dose of 100 mg fluvoxamine maleate (73.3 mg free base) in a hard gelatin capsule (subjects fasted overnight but were allowed a light breakfast 30 minutes after the administration of fluvoxamine). Observed data were reported by De Bree *et al.*, 1983.

Distribution

Plasma protein binding of fluvoxamine was reported as 86% at a concentration range of 40 to 400 nM (Yao *et al.,* 2001).

Following intravenous administration of 10 and 30 mg fluvoxamine maleate (7.3 and 22 mg free base, respectively), the volume of distribution was reported to be 24 and 23 L/kg, respectively (van Harten *et al.,* 1994). Using the same studies that were used for the optimisation of ka (Spigset *et al.,* 1998, Culm-Merdeck *et al.,* 2005), the distribution parameters were simultaneously optimised by manual sensitivity analysis altering the ka between 0.19 and 0.92 h^{-1} and the V_{ss} between 15 and 26 L/h. Distribution was best described using a SAC compartment within the minimal PBPK model with optimised values of V_{ss} (21 L/kg), V_{sac} (6 L/kg), and Q (0.5 L/h) in the SV-Fluvoxamine file.

Elimination

Fluvoxamine is extensively metabolised in the liver, primarily by CYP2D6 (Miura and Ohkubo, 2007) and exhibits non-linear kinetics (Spigset *et al.,* 1998). *In vitro* inhibition data suggest that the fraction metabolised (fm%) by CYP2D6 is 40% (Miura and Ohkubo, 2007). An *in vitro* recombinant CYP2D6 Km value from Miura and Ohkubo, 2007 was used in the SV-Fluvoxamine file. V_{max}, CL_R, and additional human liver microsomes (HLM) CL_{int} were optimised simultaneously to capture the multiple oral dose study from Spigset *et al.,* 1998. Fluvoxamine undergoes hepatic uptake, thus a generic value based on *in vitro* data was used (Guest, 2011).

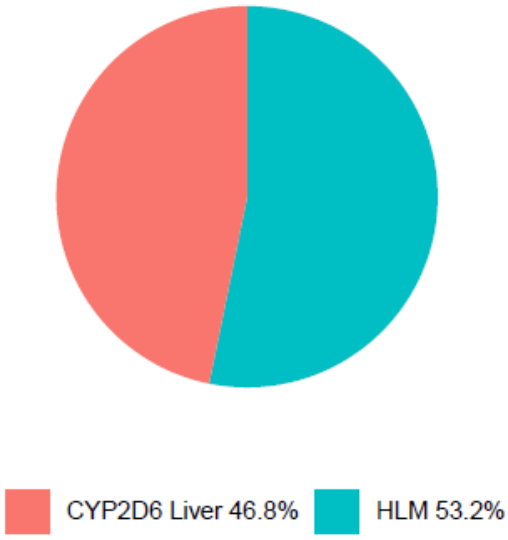

Figure 5: Predicted mean contribution of metabolic clearance to the systemic elimination of fluvoxamine using metabolic data assigned to recombinantly expressed CYP2D6. Simulations were conducted in a population of healthy male volunteers (10 trials of 20 subjects, 20-44 years; multiple oral daily doses of 100 mg of fluvoxamine maleate were simulated). The trial design was based on a clinical study by Fleishaker and Hulst, 1994.

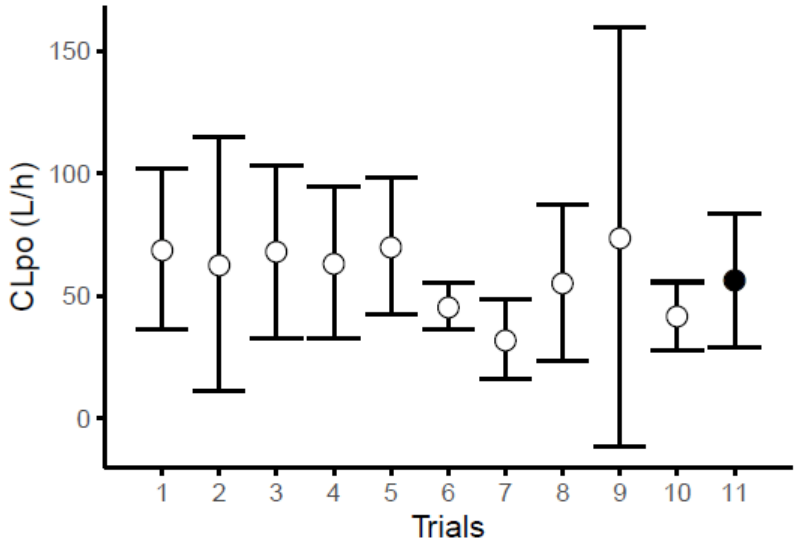

Figure 6: Simulated (◦; 10 trials of 6 subjects; 25-31 years; 50% female; fasted state) and observed (•) mean (± SD) values of CL_{po} for fluvoxamine after 50 mg fluvoxamine maleate (36.7 mg free base) oral dose in fasted state every 12 hours for 7 days. Observed data were reported by De Vries *et al.,* 1992.

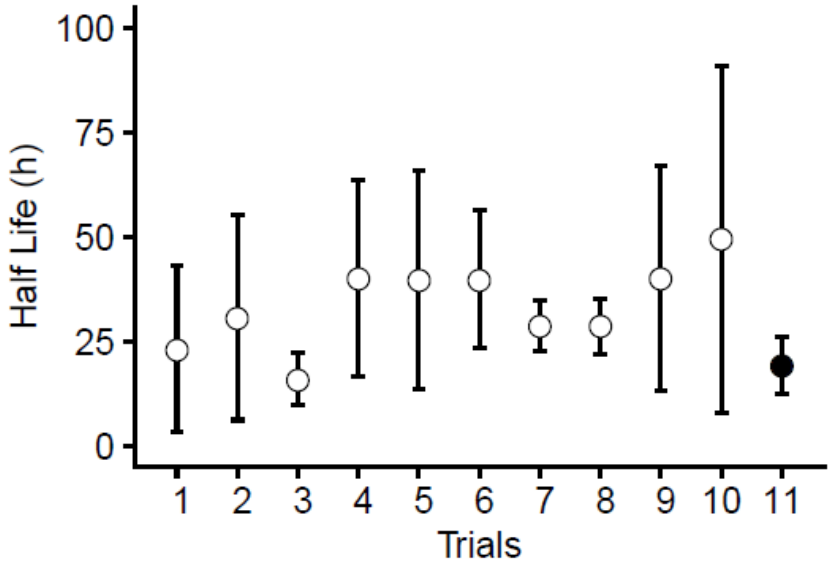

Figure 7: Simulated (◦; 10 trials of 6 subjects; 25-31 years; 50% female; fasted state) and observed (•) mean (± SD) values of half-life for fluvoxamine after 50 mg fluvoxamine maleate (36.7 mg free base) oral dose in fasted state every 12 hours for 7 days. Observed data were reported by De Vries *et al.,* 1992.

Interaction

Competitive inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP3A5 by fluvoxamine is considered in the SV-Fluvoxamine model. The CYP1A2 Ki value was optimised to capture the DDI with caffeine reported by Culm-Merdek *et al.,* 2005. Based on a publication by Yao *et al.,* 2001, it is reported that "*the fluvoxamine inhibition potency is about 10-fold greater in vivo than in vitro*." Thus, *in vitro* derived values for all the other enzymes (CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP3A5) were scaled down by 10-fold.

CYP1A2 interactions

DDI studies with the CYP1A2 substrates caffeine, theophylline, tizanidine, olanzapine, and duloxetine are shown in Tables 1 and 2. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 1. All doses of substrates and fluvoxamine were given orally, besides the intravenous application of duloxetine (Lobo *et al.*, 2008). Caffeine and theophylline were default V19 library files, tizanidine was the documented research file on the Simcyp Members Area, duloxetine was based on the compound file reported by Storelli *et al.,* 2019, and Olanzapine was based on the compound file reported by Sun *et al.,* 2020. Simulated and observed C_{max} and AUC ratios are shown in Table 2.

Table 1. Dosing regimens for CYP1A2 DDI studies

	Study	Substrate dosing	Inhibitor dosing (Fluvoxamine)
1	Culm-Merdek *et al.,* 2005[x]	Caffeine, 250 mg SD (Day 2)	100 mg (73.3 mg free base) BID for 2 days (4 doses)
2	Christensen *et al.,* 2002[a] CYP2D6 EMs and UMs	Caffeine, 100 mg SD (Day 6)	10 mg (7.33 mg free base) BID for 6 days (12 doses)
3	Christensen *et al.,* 2002[a] CYP2D6 EMs and UMs	Caffeine, 100 mg SD (Day 6)	25 mg (18.3 mg free base) BID for 6 days (12 doses)
4	Jeppesen *et al.,* 1996[c]	Caffeine 200 mg SD (Day 8)	50 mg (36.65 mg base) for 4 days followed by 100 mg (73.3 mg free base) for 8 days
5	Yao *et al.,* 2001[b]	Theophylline, 250 mg SD (Day 8 @8 AM)	25 mg (18.3 mg free base) QD for 9 days (9 doses)
6	Yao *et al.,* 2001[b]	Theophylline, 250 mg SD (Day 8 @8 AM)	50 mg (36.7 mg free base) QD on day 1, 75 mg (55 mg free base) QD days 2-9 (dosed @4 PM)
7	Orlando *et al.,* 2006[c]	Theophylline, 4 mg/kg SD (Day 6)	50 mg (36.7 mg free base) QD days 1-2, 50 mg (36.7 mg free base) BID days 3-7
8	Rasmussen *et al.,* 1997*,[c]	Theophylline 300 mg (Day 4)	50 mg (36.7 mg free base) on day 1, 100 mg (73.3 mg free base) QD for 6 days
9	Gransfors *et al.,* 2004	Tizanidine, 4 mg SD (Day 4, 1h after Fluvoxamine)	100 mg (73.3 mg free base) QD for 4 days
10	Wang *et al.,* 2004	Olanzapine 10 mg SD (Day 4)	100 mg (73.3 mg free base) daily for 9 days
11	Lobo *et al.,* 2008[#]	Duloxetine 60 mg oral dose on Day 14 and 20 (7 and 13)	50 mg on Day 1 followed by 100 mg (73.3 mg free base) for 16 days
12	Lobo *et al.,* 2008[#]	Duloxetine 10 mg IV dose on Day 14 and 20 (7 and 13)	50 mg on Day 1 followed by 100 mg (73.3 mg free base) for 16 days

[x] Used to derive an optimised CYP1A2 Ki value in the Fluvoxamine file.

* Median, [#] GeoMean, [a] $AUC_{0\text{-}24h}$, [b] $AUC_{0\text{-}48h}$, [c] AUC calculated from CL

Table 2. Observed and predicted mean C_{max} and AUC ratios for fluvoxamine interactions with CYP1A2 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**
Culm-Merdek *et al.*, 2005[x] Caffeine	1.40	13.71	1.34 (1.24 - 1.52)	12.31 (9.53 - 17.12)	0.96	0.90
Christensen *et al.*, 2002[a] Caffeine CYP2D6 EMs and UMs	1.68	2.82	1.30 (1.16 – 1.43)	3.25 (2.13 – 4.55)	0.77	1.15
Christensen *et al.*, 2002[a] Caffeine CYP2D6 EMs and UMs	2.83	5.23	1.33 (1.17 – 1.46)	3.90 (2.31 – 5.82)	0.46	0.64
Jeppesen *et al.*, 1996[c] Caffeine	-	8.36	-	12.74 (8.52 – 17.29)	-	1.52
Yao *et al.*, 2001[b] Theophylline	1.01	1.44	1.07 (1.05 – 1.08)	2.42 (2.17 – 2.84)	1.06	1.68
Yao *et al.*, 2001[b] Theophylline	1.20	2.03	1.08 (1.06 – 1.09)	2.87 (2.47 – 3.35)	0.90	1.41
Orlando *et al.*, 2006[c] Theophylline	1.11	2.66	1.08 (1.05 – 1.10)	4.01 (3.22 – 4.88)	0.97	1.51
Rasmussen *et al.*, 1997*[,c] Theophylline	-	3.33	-	3.72 (3.13 – 5.10)	-	1.12
Gransfors *et al.*, 2004 Tizanidine	12.09	32.73	9.85 (6.90 – 12.09)	32.4 (24.9 – 41.8)	0.81	0.99
Wang *et al.*, 2004 Olanzapine	1.49	1.76	1.12 (1.10 – 1.14)	1.54 (1.47 – 1.70)	0.75	0.88
Lobo *et al.*, 2008[#] Duloxetine	2.41	5.60	2.42 (2.28 – 2.74)	5.54 (4.60 – 9.91)	1.00	0.99
Lobo *et al.*, 2008[#] Duloxetine	0.84	2.70	1.01 (1.01 – 1.02)	2.39 (1.94 – 4.06)	1.20	0.89

[x] Used to derive an optimised CYP1A2 Ki value in the Fluvoxamine file.

* Median, [#] GeoMean, [a] $AUC_{0\text{-}24h}$, [b] $AUC_{0\text{-}48h}$, [c] AUC calculated from CL

CYP2C9 interactions

DDI studies with the CYP2C9 substrate tolbutamide are shown in Tables 3 and 4. 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 fluvoxamine were given orally. All substrates were default V19 library files. Simulated and observed AUC ratios are shown in Table 4.

Table 3. Dosing regimens for CYP2C9 DDI studies

	Dosage regimen	
Study	**Substrate**	**Inhibitor (Fluvoxamine)**
Madsen *et al.*, 2001	Tolbutamide, 500 mg SD on day 5 (8.00 am)	75 mg (54.98 mg free base) QD for 5 days (dosed at 8.00 pm)
Madsen *et al.*, 2001	Tolbutamide, 500 mg SD on day 5 (8.00 am)	150 mg (109.95 mg free base) QD for 5 days (dosed at 8.00 pm)

Table 4. Observed and predicted mean AUC ratios for fluvoxamine interactions with the CYP2C9 substrate tolbutamide. Predicted values show geomean 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**
Madsen *et al.*, 2001	ND	1.23	-	1.37 (1.26 – 1.43)	ND	1.12
Madsen *et al.*, 2001	ND	1.71	-	1.66 (1.48 – 1.76)	ND	0.97

ND – not determined

CYP2C19 interactions

DDI studies with the CYP2C19 substrates S-mephenytoin, omeprazole, and lansoprazole are shown in Tables 5 and 6. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 5. All doses of substrates and fluvoxamine were given orally. S-Mephenytoin and omeprazole were default V19 library files, lansoprazole was based on the file described on the Simcyp Members Area. Simulated and observed C_{max} and AUC ratios are shown in Table 6.

Table 5. Dosing regimens for CYP2C19 DDI studies

	Study	Substrate dosing	Inhibitor dosing (Fluvoxamine)
1	Yao *et al.*, 2003	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	37.5 mg (27.5 mg free base) QD for 11 days (dosed at 4 PM)
2	Yao *et al.*, 2003	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	62.5 mg (45.8 mg free base) QD for 11 days (dosed at 4 PM)
3	Yao *et al.*, 2003	S-Mephenytoin, 100 mg SD on day 9 (8 AM)	50 mg (36.7 mg free base) QD (days 1-2), 87.5 mg (64.1 mg free base) QD (days 3-11) (dosed at 4 PM)
4	Christensen *et al.*, 2002 EM	Omeprazole, 20 mg SD on day7	25 mg (18.3 mg free base) BID for 7 days
5	Christensen *et al.*, 2002 PM	Omeprazole, 20 mg SD on day7	25 mg (18.3 mg free base) QD for 7 days
6	Christensen *et al.*, 2002 EM	Omeprazole, 20 mg SD on day7	10 mg (7.32 mg free base) BID for 7 days
7	Christensen *et al.*, 2002 PM	Omeprazole, 20 mg SD on day7	10 mg (7.32 mg free base) QD for 7 days
8	Yasui-Furukori *et al.*, 2004a* EM	Omeprazole, 40 mg SD on day 6	25 mg BID (12 doses)
9	Yasui-Furukori *et al.*, 2004a* IM	Omeprazole, 40 mg SD on day 6	25 mg BID (12 doses)
10	Kamiya *et al.*, 2019* no PM	Omeprazole, 20 mg SD on day 3	25 mg (18.3 mg free base) QD for 3 days
11	Kamiya *et al.*, 2019* all subjects	Omeprazole, 20 mg SD on day 3	25 mg (18.3 mg free base) QD for 3 days
12	Yasui-Furukori *et al.*, 2004b* EMs	Lansoprazole, 40 mg SD on day 6	25 mg BID (12 doses)
13	Yasui-Furukori *et al.*, 2004b* IM1s	Lansoprazole, 40 mg SD on day 6	25 mg BID (12 doses)

* In Japanese

Table 6. Observed and predicted mean C_{max} and AUC ratios for fluvoxamine 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**
Yao *et al.*, 2003	2.12	4.64	2.15 (1.97 – 2.42)	5.41 (4.66 – 6.90)	1.01	1.17
Yao *et al.*, 2003	2.40	6.70	2.45 (2.20 – 2.82)	8.21 (7.09 – 10.4)	1.02	1.22
Yao *et al.*, 2003	2.42	9.89	2.64 (2.34 – 3.08)	10.99 (9.47 – 13.86)	1.09	1.11
Christensen *et al.*, 2002* EM	ND	5.46	2.79 (2.09 – 3.75)	4.86 (3.36 – 7.10)	ND	0.89
Christensen *et al.*, 2002* PM	ND	5.85	2.90 (2.09 – 3.80)	5.34 (3.43 – 7.25)	ND	0.91
Christensen *et al.*, 2002* EM	ND	2.63	2.21 (1.82 – 2.81)	3.15 (2.42 – 4.20)	ND	1.20
Christensen *et al.*, 2002* PM	ND	2.43	2.32 (1.83 – 2.85)	3.46 (2.63 – 4.29)	ND	1.42
Yasui-Furukori *et al.*, 2004a[#,*] EM	3.48	5.34	2.73 (2.28 – 3.26)	5.07 (3.75 – 6.64)	0.78	0.95
Yasui-Furukori *et al.*, 2004a[#,*] IM	1.91	2.26	2.23 (1.94 – 2.55)	3.68 (2.80 – 4.58)	1.17	1.63
Kamiya *et al.*, 2019[#,*] no PM	1.91	2.73	2.33 (2.18 – 2.72)	3.88 (3.53 – 4.71)	1.18	1.35
Kamiya *et al.*, 2019[#,*] all subjects	1.70	2.26	2.00 (1.58 – 2.34)	3.05 (2.02 – 3.95)	1.18	1.35
Yasui-Furukori *et al.*, 2004b EMs	1.54	3.83	1.68 (1.46 – 1.85)	4.43 (3.52 – 5.83)	1.09	1.16
Yasui-Furukori *et al.*, 2004b IM1s	1.21	2.50	1.48 (1.36 – 1.57)	3.60 (2.96 – 4.39)	1.22	1.44

[#] GeoMean, * $AUC_{0\text{-}8h}$

CYP2D6 interactions

DDI studies with the CYP2D6 substrates atomoxetine, nebivolol, dextromethorphan, desipramine, and imipramine are shown in Tables 7 and 8. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 7. All doses of substrates and fluvoxamine were given orally. Atomoxetine, dextromethorphan, and desipramine were default V19 library files. Nebivolol and imipramine were based on the corresponding compound files described on the Simcyp Members Area. Simulated and observed C_{max} and AUC ratios are shown in Table 8.

Table 7. Dosing regimens for CYP2D6 DDI studies

	Study	Substrate dosing	Inhibitor dosing (Fluvoxamine)
1	Todor *et al.*, 2017~	Atomoxetine, 25 mg (Day 6 at 9.00 am)	50 mg (36.7 mg free base) QD days 1-3, 100 mg (73.3 mg free base) QD days 4-6, at 9.00 am
2	Gheldiu *et al.*, 2017 EMs and UMs	Nebivolol, 5 mg (4.6 mg free base) on day 8	50 mg (36.7 mg free base) QD days 1-3, 100 mg (73.3 mg free base) QD days 3-7
3	Miura *et al.*, 2021*	Dextromethorphan 30 mg SD day 2	25 mg (18.3 mg free base) BID 3 doses
4	Spina *et al.*, 1993~	Desipramine 100 mg (82.5 mg free base) SD on day 7 (dosed at 8.00 am)	100 mg (73.3 mg free base) QD for 10 days (dosed at 8.00 pm)
5	Spina *et al.*, 1993~	Imipramine 50 mg (44.26 mg free base) SD on day 7	100 mg (73.3 mg free base) QD for 10 days (dosed at 8.00 pm)

* In Japanese, ~ No CYP2D6 PMs, thus only EMs, IMs, and UMs were simulated.

Table 8. Observed and predicted mean C_{max} and AUC ratios for fluvoxamine interactions with CYP2D6 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
Todor *et al.*, 2017~	1.25	1.33	1.27 (1.24 – 1.33)	1.47 (1.40 – 1.53)	1.02	1.10
Gheldiu *et al.*, 2017 EMs and UMs	1.32	1.57	1.67 (1.61 – 1.73)	1.61 (1.56 – 1.66)	1.27	1.03
Miura *et al.*, 2021*	-	1.33	1.31 (1.28 – 1.33)	1.32 (1.29 – 1.34)	-	0.99
Spina *et al.*, 1993~ Desipramine	1.04	1.14	1.30 (1.25 – 1.33)	1.45 (1.40 – 1.53)	1.24	1.27
Spina *et al.*, 1993~ Imipramine[#]	2.27	3.63	1.90 (1.68 – 2.23)	3.20 (2.56 – 4.24)	0.84	0.88

* In Japanese, ~ No CYP2D6 PMs, thus only EMs, IMs, and UMs were simulated, [#]Additional CYP2C19 inhibition is accounted for, and the metabolite was activated in the simulation.

CYP3A4 interactions

DDI studies with the CYP3A4 substrates alprazolam, midazolam, and quinidine are shown in Tables 9 and 10. The trial designs used were based on the clinical studies and the dosing regimen for each study is shown in Table 9. All doses of substrates and fluvoxamine were given orally. All substrates were default V19 library files. Simulated and observed C_{max} and AUC ratios are shown in Table 10.

Table 9. Dosing regimens for CYP3A4 DDI studies

	Study	Substrate dosing	Inhibitor dosing (Fluvoxamine maleate)
1	Fleishaker and Hulst, 1994	Alprazolam 1 mg oral QD from day 7 to day 10, at 8:00, 13:00, 18:00, and 23:00	50 mg (36.65 mg free base) oral QD from day 1 to day 3 at 8:00, and 100 mg (73.33 mg free base) oral QD from day 4 to day 10 at 8:00
2	Chen *et al.*, 2006	Midazolam, 0.025 mg/kg SD IV on day 28	150 mg (109.95 mg free base) QD oral for 28 days
3	Lam *et al.*, 2003	Midazolam 10 mg SD on day 12 (1h after fluvoxamine)	50 mg (36.65 mg free base) BID days 1-6, 100mg (73.33 mg free base) BID days 7-12
4	Damkier *et al.*, 1999	Quinidine, 166 mg free base, single dose, oral, day 5	100 mg (73.33 mg free base), QD, oral, 6 days

Table 10. Observed and predicted mean C_{max} and AUC ratios for fluvoxamine interactions with CYP3A4 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
Fleishaker and Hulst, 1994	1.86	1.96	1.06 (1.05 – 1.08)	1.08 (1.06 – 1.11)	0.57	0.55
Chen *et al.*, 2006	ND	1.49	1.44 (1.37 – 1.49)	1.57 (1.48 – 1.65)	ND	1.06
Lam *et al.*, 2003	1.38	1.39	1.21 (1.18 – 1.27)	1.31 (1.23 – 1.41)	0.88	0.94
Damkier *et al.*, 1999	1.35	1.41	1.08 (1.07 – 1.11)	1.17 (1.13 – 1.22)	0.80	0.83

Input Parameters

Table 11: Input Table

Parameter	Value	Method/Reference
Molecular weight (g /mol)	318.3	PubChem 2019
log P	3	Meta-analysis (El Ela *et al.,* 2004; CHEAMBL814 AlogP and CX LogP, and PubChem X LogP3-AA)
Compound type	Monoprotic Base	
pK_a	8.7	Foda *et al.,* 1996
B/P	1.5	Simcyp data archive, Consortium member data, unpublished measured data on file
fu_p	0.14	Yao *et al.,* 2001
Main plasma binding protein	Human serum albumin	Simcyp data archive, Consortium member data, unpublished measured data on file
fa	1	
Ka (1/h)	0.7	Optimised - see Absorption section for details
fu_{gut}	0.14	Same as fu_p
Q_{gut}	15.87	Predicted (Yang *et al.,* 2007)
Distribution Model	Minimal PBPK model	
V_{ss} (L/kg)	21	Optimised with SAC - see Distribution section
Q (L/h)	0.50	Optimised with SAC - see Distribution section
V_{sac} (L/kg)	6.0	Optimised with SAC - see Distribution section
Enzyme	CYP1A2	
K_I (µM)	0.002	Optimised - strong CYP1A2 Ki. A clinical DDI study with caffeine using the fluvoxamine 100 mg BID dosage regimen (Culm-Merdek *et al.,* 2005) was used.
Enzyme	CYP2C9	
K_I (µM)	0.126	Optimised - weak CYP2C9 Ki. Original value derived from meta-analysis of *in vitro* HLM data (Schmider *et al.,* 1997; Hemeryck *et al.,* 1999). The value was lowered ten-fold as ten-fold difference between *in vitro* and *in vivo* Ki for fluvoxamine reported (Yao *et al.,* 2001).
Enzyme	CYP2C19	
K_I (µM)	0.006	Optimised - strong CYP2C19 Ki. Original value derived from *in vitro* HLM data (Yao *et al.,* 2003). Value lowered ten-fold as ten-fold difference between *in vitro* and *in vivo* Ki for fluvoxamine was reported (Yao *et al.,* 2001).
Enzyme	CYP2D6	
V_{max} (pmol/min/pmol)	70	Optimised - Spigset *et al.,* 1998, multiple oral dose study
Km (µM)	38.6	Miura and Ohkubo, 2007
K_I (µM)	0.189	Optimised - weak CYP2D6 Ki. Original value derived from meta-analysis of *in vitro* HLM data (Ball *et al.,* 1997; Belpaire *et al.,* 1998, Crewe *et al.,* 1992; Fogelman *et al.,* 1999; Nielsen *et al.,* 1996; Otton *et al.,* 1993; Otton *et al.,* 1994; Otton *et al.,* 1996; von Moltke *et al.,* 1995). Value lowered ten-fold as ten-fold difference between *in vitro* and *in vivo* Ki for fluvoxamine reported (Yao *et al.,* 2001).
CL_{int} (HLM) (µL/min/mg protein)	14	Optimised - Spigset *et al.,* 1998, multiple oral dose study

Enzyme	CYP3A4	
K_I (µM)	0.789	Optimised - moderate CYP3A4 Ki. Original value derived from meta-analysis of *in vitro* data (Iribarne *et al.,* 1998; von Moltke *et al.,* 1995; von Moltke *et al.,* 1996a; von Moltke *et al.,* 1996b). Value lowered ten-fold as ten-fold difference between *in vitro* and *in vivo* Ki for fluvoxamine reported (Yao *et al.,* 2001).
Enzyme	CYP3A5	
K_I (µM)	5.82	Optimised - moderate CTP3A5 Ki. Ten-fold reduction on *in vitro* Ki (Yao *et al.,* 2001).
Active Hepatic Scalar (Net)	3	Guest, 2011

What is not currently considered in the model

• Inhibition of CYP2C8.
It should be noted that none of the substrates evaluated for DDI potential in this compound summary are classified as a CYP2C8 substrate (Certara Dug interaction solutions database).

• Inhibition of P-gp.
It should be noted that none of the substrates evaluated for DDI potential in this compound summary are classified as a P-gp substrate (Certara Dug interaction solutions database).

• The pharmacodynamics of fluvoxamine have not been investigated and incorporated into the file.

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