7 Appendix

7.1 Table of all PK and Bioequivalence studies (direct excerption from the submission)

Protocol	Study Description
M/2000/0214	Bioavailability and in vivo-release characteristics of 4 prototype XR 1-mg tablet formulations.
M/2000/0235	Bioavailability of 4 prototype XR 1-mg tablet formulations.
M/2000/0242	Bioavailability of 3 prototype XR 2-mg tablet formulations.
M/2000/0243	Bioavailability of 3 prototype XR 3-mg tablet formulations.
M/2000/0253	Single- and multiple-dose pharmacokinetic and pharmacodynamic study of 1-, 3-, and 6-mg doses of XR tablets.
M/2000/0275	Effects of food on the bioavailability of XR 1-mg tablets.
M/2000/0305	Bioequivalence of international 1-mg XR tablets.
M/2000/0346	Bioequivalence of international 1-mg XR tablets.
M/2000/0352	Bioequivalence of 1-, 2-, and 3-mg XR tablets.
P/2002/0001	Effects of in vitro dissolution rate on the bioavailability of XR tablets.
R/2002/0001	Bioavailability of XR 0.25-, 0.5-, and two 1-mg tablet formulations.
R/2002/0002	Pharmacokinetics and pharmacodynamics of alprazolam at steady-state after once daily administration of XR tablets and four times daily administration of alprazolam compressed tablets.
R/2002/0003	Single-dose pharmacokinetic and pharmacodynamic study to evaluate the dose proportionality of XR tablets.

Protocol	Study Description
P/2002/0007	Pharmacokinetics of alprazolam after morning versus bedtime administration of XR tablets.
P/2002/0008	Effects of in vivo release rate on the abuse liability of alprazolam
P/2002/0010	Pharmacokinetics and pharmacodynamics of alprazolam at steady-state after twice daily administration of XR tablets and four times daily administration of alprazolam compressed tablets.
P/2002/0013	Effects of food on the bioavailability of XR 3-mg tablets.
P/2002/0016	Effects of in vitro dissolution rate on the bioavailability of XR tablets.
P/2002/0017	Pharmacokinetics and pharmacodynamics of alprazolam relative to meal timing
P/2002/0018	Bioequivalence of XR tablets sourced from Puerto Rico and the U.S.
M/2002/0020	Steady-state plasma alprazolam concentrations in relationship to effects on psychomotor performance and EEG changes
M/2002/0037	Steady-state pharmacokinetics and pharmacodynamics (EEG and DSST) of alprazolam following the administration of immediate release and XR tablets
M/2002/0044	Pharmacokinetic and pharmacodynamic evaluation of alprazolam XR, bromazepam and lorazepam

Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{∞} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
M/2000/0214	A = 1 XR 1-mg tab (Lot No. 23,028)	1	1	30	120 (20)§	6.41 (1.21)	9.66 (5.7)	—	—	—	6
	B = 1 XR 1-mg tab (Lot No. 23,029)	1	1	30	131 (26)§	8.23(1.94)	9.03 (3.5)	—	—	—	
	C = 1 XR 1-mg tab (Lot No. 23,030)	1	1	30	104 (21)§	5.64(1.0)	14.8 (5.7)	—	—	—	
	D = 1 XR 1-mg tab (Lot No. 23,031)	1	1	30	110 (24)§	6.21(1.4)	15.9 (5.8)	—	—	—	
	E = 1 IR 1-mg tab (Lot No. 205RF)	1	1	30	154 (35)	13.9 (3.0)	1.57 (0.85)	—	—	—	
M/2000/0235	A = 1 XR 1-mg tab (Lot No. 23,435; #7R)	1	1	28	220 (59.7)	10.9(1.82)	4.25(1.04)	10.7	—	—	7
	B = 1 XR 1-mg tab (Lot No. 23,436; #12)	1	1	28	220 (69.9)	8.67(1.47)	5.89 (2.78)	10.7	—	—	
	C = 1 XR 1-mg tab (Lot No. 23,437; #14)	1	1	28	223 (70.7)	8.97 (1.78)	6.64 (2.18)	10.5	—	—	
	D = 1 XR 1-mg tab (Lot No. 23,438; #15)	1	1	28	220 (62.5)	8.72 (1.31)	7.79 (3.71)	10.5	—	—	
	E = ALP soln 1 mg IV (Lot No. 23,453)	1	1	28	**	**	**	**	**	**	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_s); for oral administration, apparent oral clearance corrected for body weight (Cl_{po}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.

Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{∞} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
M/2000/0253	A = ALP soln 1 mg IV	1	1	41	279 (94.9)	18.6 (9.76)	0.18 (0.04)	12.0	—	53.1 (16.7)**	11
	B = 1 XR 1-mg tab	1	1	13	230 (96.6)	7.82 (1.71)	8.08 (3.12)	13.9	—	74.2 (39.8)**	
	1 XR 1-mg tab QD x 3 d	1	3	13	240 (61.8)¶	13.0 (2.92)¶	5.46(2.99)	16.5	—	60.9 (16.4)**	
	C = 3 XR 1-mg tab	3	1	14	651 (235)	24.9 (9.38)	6.71 (1.49)	13.3	—	69.6 (23.6)**	
	3 XR 1-mg tab QD x 3 d	3	3	14	678 (265)¶	38.3 (14.2)¶	6.82 (7.19)	15.1	—	67.1 (21.9)**	
	D = 6 XR 1-mg tab	6	1	12	1587 (395)	50.3 (7.5)	9.33 (3.45)	15.8	—	51.7 (12.9)**	
	6 XR 1-mg tab QD x 3 d	6	3	12	1527 (391)¶	86.3 (20.8)¶	4.42 (1.51)	15.1	—	53.7 (12.5)**	
M/2000/0275	A = 1 XR 1-mg tab (fasting)	1	1	21	229.2 (26)¶	8.2 (10)††	7.2 (39)††	13.1	—	—	15
	B = 1 XR 1-mg tab (after meal)	1	1	21	212.3 (27)¶	9.2 (17)††	7.0 (31)††	11.2	—	—	
	C = 1 IR 1-mg tab (fasting)	1	1	21	217.3 (33)¶	13.4 (18)††	1.5 (49)††	12.1	—	—	
M/2000/0505	A = 1 XR 1-mg tab (Lot No. 85,317)	1	1	22	200 (56.3)	7.44(1.82)	6.88 (3.77)	11.4	—	—	13
	B=1 XR 1-mg tab (Lot No. 35,052)	1	1	22	204 (59.1)	9.00(1.66)	5.71 (2.63)	11.0	—	—	
	C = 1 IR 1-mg tab (Lot No. 873RH)	1	1	22	204 (57.1)	14.3 (3.04)	1.35 (0.824)	11.4	—	—	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_s); for oral administration, apparent oral clearance corrected for body weight (Cl_{po}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
** Not reported; used only to calculate absolute bioavailability.
*** Not reported; used only to calculate relative bioavailability

Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC$_{inf}$ (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
M/2000/0242	A = 1 XR 2-mg tab (Lot No. 24,092; #12)	2	1	24	457 (139)	16.1 (2.68)	8.38 (4.30)	11.7	—	—	8
	B = 1 XR 2-mg tab (Lot No. 24,091; #7R)	2	1	24	451 (87.3)	18.8 (3.46)	5.46 (2.26)	12.6	—	—	
	C = 1 XR 2-mg tab (Lot No. 24,093; #10)	2	1	24	426 (119)	12.7 (2.45)	12.0 (4.93)	12.4	—	—	
	D = 1 XR 1-mg tab (Lot No. 85,317; #12)	1	1	24	231 (59.6)	8.02 (1.62)	9.25 (2.94)	12.6	—	—	
	E = 1 IR 1-mg tab (Lot No. O13YH)	1	1	24	***	***	***	***	—	—	
M/2000/0243	A = 1 XR 3-mg tab (Lot No. 24,095; #12)	3	1	23	675 (185)	23.6 (4.90)	8.83 (4.48)	12.6	—	—	9
	B = 1 XR 3-mg tab (Lot No. 24,094; #7R)	3	1	23	638 (178)	29.0 (7.79)	4.39 (1.03)	11.9	—	—	
	C = 1 XR 3-mg tab (Lot No. 24,096; #10)	3	1	23	632 (186)	18.2 (3.99)	10.7 (5.21)	13.1	—	—	
	D = 1 XR 1-mg tab (Lot No. 85,317; #12)	1	1	23	201 (58.8)	7.83 (2.05)	7.13 (4.93)	11.4	—	—	
	E = 1 IR 1-mg tab (Lot No. PM4658)	1	1	23	***	***	***	***	***	***	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl$_{tot}$); for oral administration, apparent oral clearance corrected for body weight (Cl/F$_{tot}$).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
** Not reported; used only to calculate absolute bioavailability.
*** Not reported; used only to calculate relative bioavailability

Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC$_{inf}$ (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
M/2000/0346	A = 1 XR 1-mg tab (Lot No. 85317)	1	1	24	265 (67.7)	9.06(1.64)	7.53 (3.16)	14.4	—	—	14
	B = 1 XR 1-mg tab (Lot NO. 35,283)	1	1	24	267 (69.8)	8.68 (1.76)	7.46 (4.14)	14.1	—	—	
	C = 1 ACC 1-mg tab (Lot No. 87,3RH)	1	1	24	270(63.0)	15.4(2.03)	1.60 (0.969)	13.0	—	—	
M/2000/0352	A = 2 XR 3-mg tab (Lot No. 24,095)	6	1	24	1194 (284)	43.5 (6.33)	8.64 (3.92)	11.7	1.23 (0.167)	1.19 (0.332)	40
	B = 3 XR 2-mg tab (Lot No. 24,092)	6	1	24	1131 (282)	42.7 (10.5)	8.64 (3.05)	11.7	1.28 (0.234)	1.26 (0.394)	
	C = 6 XR 1-mg tab (Lot No. 85,317)	6	1	24	1174 (224)	44.3 (8.03)	8.09 (2.72)	11.7	1.20 (0.171)	1.19 (0.297)	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl$_{tot}$); for oral administration, apparent oral clearance corrected for body weight (Cl/F$_{tot}$).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
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Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{inf} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
P/2002/0001	A = 1 XR 1-mg tab (Lot No. 35,890;slow release)	1	1	25	246(63-5)	7.96(1.49)	9.36 (3.40)	14.7	1.19 (0.242)	0.924 (0.277)	41
	B = 1 XR 1-mg tab (Lot No. 35,889; fast release)	1	1	25	245 (50.6)	9.43(1.44)	8.00 (2.08)	13.6	1.06 (0.140)	0.905 (0.219)	
	C = 1 XR 3-mg tab (lot No. 35,892; slow release)	3	1	25	782 (185)	22.6 (3.35)	11.1 (3.26)	15.7	1.17 (0.164)	0.857 (0.212)	
	D = 1 XR 3-mg tab (Lot No. 35,891; fast release)	3	1	25	763 (172)	27.6 (4.70)	7.92 (2.41)	14.4	1.11 (0.175)	0.882 (0.242)	
	E = 1 XR 1-mg tab (Lot No. 35,888; target release)	1	1	25	251 (63.6)	8.35(1.48)	9.04 (2.24)	14.1	1.11 (0.166)	0.898 (0.259)	
R/2002/0001	A = 4 XR 0.25-mg tab (Lot No. 35,561)	1	1	24	211 (64.7)	7.60 (1.31)	7.00 (2.77)	11.9	—	—	10
	B = 2 XR 0.5-mg tab (Lot No. 35,562)	1	1	24	206 (58.8)	7.28(1.33)	6.92 (2.89)	12.4	—	—	
	C = 1 XR 1-mg tab (Lot No. 35,563)	1	1	24	218 (69.5)	7.84(1.82)	7.67 (3.84)	12.1	—	—	
	D = 1 XR 1-mg tab (Lot No. 35,565)	1	1	24	216(78.4)	7.45(1.26)	8.17 (2.94)	12.1	—	—	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_s); for oral administration, apparent oral clearance corrected for body weight (Cl_{po}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
◆◆ Not reported; used only to calculate absolute bioavailability.
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Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{inf} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
R/2002/0002	A = 2 XR 3-mg tab	6	1	20	1167 (287)	45.3 (7.78)	10.0 (3.61)	11.2	1.15 (0.171)	1.19 (0.322)	16
	2 XR 3-mg tab QD x 6 d	6	6	20	1285 (407)¶	70.9 (17.7)¶	6.75 (1.97)	11.7	1.15 (0.186)	1.12 (0.372)	
	B = 1 IR 1-mg tab + 1 IR 0.5-mg tab	1.5	1	20	312 (116)	22.0 (6.63)	1.70 (1.51)	10.3	1.03 (0.156)	1.4 (0.281)	
	1 IR 1-mg tab + 1 IR 0.5-mg tab QID x 6 d	1.5‡‡	24	20	1298 (442)¶	70.3 (20.6)¶	9.15 (4.58)	11.4	1.10 (0.141)	1.11 (0.345)	
R/2002/0003	B = 1 XR 2-mg tab	2	1	24	443 (190)	15.1 (4.02)	11.0 (3.50)	12.8	1.19 (0.196)	1.08 (0.272)	38
	C = 2 XR 2-mg tab	4	1	24	920 (475)	31.5 (10.3)	9.76 (3.13)	13.3	1.22 (0.175)	1.05 (0.253)	
	D = 4 XR 2-mg tab	8	1	24	1800 (636)	62.8 (11.1)	9.48 (3.43)	13.1	1.21 (0.148)	1.05 (0.276)	
	E = 5 XR 2-mg tab	10	1	24	2142 (611)	70.5 (13.2)	9.38 (3.77)	13.6	1.26 (0.111)	1.07 (0.246)	
P/2002/0007	A = 1 IR 1-mg tab at 7:00 AM	1	1	24	244 (57.7)	14.4 (2.46)	1.59 (0.875)	12.4	0.99 (0.116)	0.927 (0.228)	39
	B = 3 XR 1-mg tab at 7:00 AM	3	1	24	750 (186)	23.3 (3.67)	9.91 (2.21)	14.7	1.15 (0.124)	0.906 (0.219)	
	C = 1 IR 1-mg tab at 10:00 PM	1	1	24	261 (69)	13.1 (4.68)	3.61 (2.95)	12.6	0.953 (0.139)	0.882 (0.259)	
	D = 3 XR 1-mg tab at 10:00 PM	3	1	24	768 (189)	30.2 (4.9)	8.61 (1.53)	13.3	1.01 (0.145)	0.887 (0.230)	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_s); for oral administration, apparent oral clearance corrected for body weight (Cl_{po}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
◆◆ Not reported; used only to calculate absolute bioavailability.
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Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{∞} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
P/2002/0010	A = 1 IR 1-mg tab + 1 IR 0.5-mg tab	1.5	1	20	359 (154)	21.7 (5.15)	1.82(1.07)	10.0	0.964 (0.171)	1.12 (0.377)	17
	B = 1 XR 3-mg tab	3	1	20	757 (421)	25.1 (6.89)	9.88 (4.09)	12.4	1.16 (0.162)	1.12 (0.429)	
	C = 1 IR 1-mg tab + 1 IR 0.5-mg tab QID x 7 d	1.5‡‡	28	20	1514 (596)**	82.9 (28.8)	7.24 (3.32)	12.6	112 (0.137)	1.04 (0.331)	
	D = 1 XR 3-mg tab BID x 7 d	3‡‡	14	20	1574 (610)**	84.1 (35.8)	10.1 (6.81)	13.3	1.14 (0.172)	1.00 (0.334)	
P/2002/0013	A = 1 XR 3-mg tab (fasting)	3	1	21	610 (208)	21.7 (4.42)	10.6 (3.23)	11.7	1.22 (0.197)	1.21 (0.359)	18
	B = 1 XR 3-mg tab (after meal)	3	1	21	586 (177)	27.4 (4.83)	6.95 (1.36)	10.8	1.17 (0.116)	1.23 (0.345)	
	C = 1 IR 1-mg tab (fasting)	1	1	21	192 (61.5)	13.7 (4.71)	2.03 (2.49)	9.76	1.07 (0.125)	1.27 (0.351)	
P/2002/0016	A = 1 XR 0.5 mg Tablet (-25% HPMC, Res. No. 26,243)	0.5	1	25	122 (32.0)	4.68 (0.734)	6.96 (1.31)	14.4	1.21 (0.167)	0.971 (0.280)	42
	B = 1 XR 0.5 mg Tablet (-15% HPMC, Res. No. 26,244)	0.5	1	25	117 (35.9)	4.16 (0.668)	8.00 (1.91)	13.9	1.27 (0.266)	1.04 (0.356)	
	C = 1 XR 0.5 mg Tablet (Target, Res. No. 26,245)	0.5	1	25	118 (30.8)	3.97 (0.688)	8.56 (3.54)	13.6	1.21 (0.262)	1.01 (0.366)	
	D = 1 XR 0.5 mg Tablet (+15% HPMC, Res. No. 26,246)	0.5	1	25	125 (39.0)	3.95 (0.828)	9.24 (4.17)	14.7	1.28 (0.362)	0.990 (0.373)	
	E = 1 XR 0.5 mg Tablet (+25% HPMC, Res. No. 26,247)	0.5	1	25	120 (37.4)	3.68 (0.674)	11.4 (4.30)	14.1	1.27 (0.257)	1.04 (0.414)	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_B); for oral administration, apparent oral clearance corrected for body weight (Cl_{OB}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
** Not reported; used only to calculate absolute bioavailability.
***Not reported; used only to calculate relative bioavailability

Table 5.1. In Vivo Study Data Summary
Pharmacokinetic/Bioavailability/Bioequivalence Studies with Alprazolam Sustained-Release Tablets
Mean Value (Standard Deviation) for Alprazolam Pharmacokinetic Parameters

Protocol No.	Treatment*	Dose (mg)	No. Doses	No. Subjects	AUC_{∞} (ng-h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)†	Vd/F (L/kg)	Clearance (mL/min/kg)‡	Ref. No.
P/2002/0017	A = 1 XR 3 mg Tablet one hour before meal	3	1	29	683 (206)	22.8 (4.26)	10.6 (4.06)	13.9	1.30 (0.280)	1.09 (0.376)	37
	B = 1 XR 3 mg Tablet immediately after meal	3	1	29	688 (185)	29.1 (4.82)	7.52 (2.05)	12.6	1.17 (0.158)	1.07 (0.364)	
	C = 1 XR 3 mg Tablet one hour after meal	3	1	29	655 (165)	27.4 (4.81)	6.41 (0.983)	13.1	1.25 (0.169)	1.11 (0.342)	
	D = 1 XR 3 mg Tablet two hours after meal	3	1	29	662 (161)	29.0 (5.43)	6.69 (1.34)	12.6	1.18 (0.124)	1.09 (0.329)	
	E = 1 XR 3 mg Tablet while fasting	3	1	29	707 (200)	23.9 (4.46)	8.10 (3.07)	13.9	1.24 (0.199)	1.05 (0.357)	
P/2002/0018	A = 1 XR 3 mg Tablet (Kalamazoo, Res. No. 26,379)	3	1	24	920 (225)	30.7 (6.86)	10.9 (4.89)	13.6	0.881 (0.129)	0.742 (0.206)	43
	B = 1 XR 3 mg Tablet (Puerto, Rico, Res. No. 26,437)	3	1	24	926 (205)	31.5 (4.58)	9.58 (3.34)	13.3	0.844 (0.088)	0.726 (0.166)	
M/2002/0020	A = 2 IR 0.5-mg tab	0.5	1	17	150 (75.2)	8.23 (1.29)	1.56 (0.705)	18.9	0.944 (0.145)	0.845 (0.293)	44
	1IR 0.25 mg tab QID x 4 d	0.25	16	17	301 (120)¶	15.1 (5.12)	11.6 (7.11)	20.8	1.03 (0.186)	0.800 (0.242)	
	B = 1 XR 0.5-mg tab0.5-mg tab	0.5	1	17	188 (67.3)	5.02 (0.916)¶	7.76 (3.53)¶	28.6	1.10 (0.269)	0.633 (0.197)	
	1 XR 0.5-mg tab Q12h x 4 d	0.5	8	17	322 (99.7)¶	16.1 (4.65)¶	12.6 (6.83)¶	20.8	0.939 (0.133)	0.726 (0.201)	

*XR = alprazolam sustained-release; IR = alprazolam compressed tablet (immediate release); ALP = alprazolam; tab = tablet; soln = solution; IV = intravenously; QD = once daily, BID = twice daily; QID = four times daily.
†Harmonic mean.
‡For IV administration, systemic clearance corrected for body weight (Cl_B); for oral administration, apparent oral clearance corrected for body weight (Cl_{OB}).
§0-24 h.
¶For one dosing interval at steady-state.
**Clearance is expressed in mL/h-kg.
††Coefficient of variation (%).
‡‡Total daily dose, 6 mg.
— Not calculated.
** Not reported; used only to calculate absolute bioavailability.
***Not reported; used only to calculate relative bioavailability

7.2 Review of New Individual study and new information submitted in current NDA

7.2.1 P/2002/0017: The influence of meal timing on the PK and PD of Xanax XR tablets

(This synopsis is a direct excerpt from the submission)

Name of Company: Pharmacia & Upjohn Name of Finished Product: XANAX® XR Tablets Name of Active Ingredient: Alprazolam	Individual study table referring to part of the dossier Volume: 25 Page: 141	(For National authority use only)

Protocol P/2002/0017
Bioequivalence Study

Title of Study: The Influence of Meal Timing on the Pharmacokinetics and Pharmacodynamics of XANAX XR® Tablets (P/2002/0017)

Clinical Phase: I **Study Period:** January 10, 1992-March 16, 1992.

Technical Report: [redacted] The Influence of Meal Timing on the Pharmacokinetics and Pharmacodynamics of XANAX XR® Tablets (P/2002/0017). Upjohn Technical Report 7215-93-050, November 30, 1993.

Investigator and Study Site: [redacted]

Publication: None

Study Objective: To assess the effect of meal timing on the pharmacokinetics and pharmacodynamics of alprazolam after the administration of XANAX XR Tablets.

Study Design: Open label, five-way crossover study.

Test Drug:
Treatment A: One 3 mg XANAX XR Tablet, one hour before meal (Res. No. 26,290)
Treatment B: One 3 mg XANAX XR Tablet, immediately after meal (Res. No. 26,290)
Treatment C: One 3 mg XANAX XR Tablet, one hour after meal (Res. No. 26,290)
Treatment D: One 3 mg XANAX XR Tablet, two hours after meal (Res. No. 26,290)
Treatment E: One 3 mg XANAX XR Tablet, while fasting (Res. No. 26,290)

Inclusion criteria: Healthy volunteers, ages 18-55.

Number of Subjects and Dropouts: 31 enrolled, 2 dropouts

Sampling Times: Blood samples were collected at 0 hour (just before dosing) and 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48 h after dosing

Statistical Methods: Pharmacokinetic parameters were determined by noncompartmental techniques. Differences among treatments were assessed by analysis of variance. Bioequivalence was assessed by two-one sided t-test analysis of log transformed data.

Name of Company: Pharmacia & Upjohn Name of Finished Product: XANAX® XR Tablets Name of Active Ingredient: Alprazolam	Individual study table referring to part of the dossier Volume: 1 Page: 85	(For National authority use only)

Results:

Mean (±standard deviation) alprazolam pharmacokinetic parameters following the administration of 3 mg XANAX XR Tablets at different times relative to a standard high fat breakfast to 29 healthy volunteers

	Treatment					
Parameter	A	B	C	D	E	ANOVA p-value
AUC (ng hr/ml)	683 (208)	688 (185)	655 (165)	662 (161)	707 (200)	0.0500
Cmax (ng/ml)	22.8* (4.26)	29.1† (4.82)	27.4‡ (4.81)	29.0† (5.43)	23.9* (4.46)	0.0001
Tmax (hr)	10.6* (4.06)	7.52† (2.05)	6.41‡ (0.983)	6.69†, ‡ (1.34)	8.10† (3.07)	0.0001

*, †, ‡ Values with different superscript symbols are significantly different at $p<0.05$ by Waller-Duncan k-ratio t test.

There were significant differences in Cmax and Tmax between the pre-meal and fasting treatments and the post-meal treatments. The increase in Cmax for the post-meal treatments ranged from 14.6% to 21.8% compared to the fasting treatment. Tmax occurred between 7.16% and 20.9% earlier for the post-meal treatments and 30.9% later for the pre-meal treatment compared to the fasting treatment. Psychomotor performance decrement was greater for the post-meal treatments, although variability precluded prediction of maximum performance decrement from Cmax for an individual.

Adverse Medical Events: No serious adverse events were reported. Seventy-eight non-serious medical events were recorded. The most common adverse effects experienced in this study were tiredness, sleepiness, headache, and lightheadedness. None of these events were unexpected for single doses of alprazolam.

Conclusions: Considering the magnitude of increased Cmax and the fact that tolerance develops to the sedative effects of alprazolam after multiple dosing, the clinical consequences of these results would likely be minimal.

Table 6. Mean (± standard deviation) Alprazolam Pharmacokinetic Parameters Resulting From Single Oral Doses of 3 mg XANAX XR Tablets Administered at Different Times Relative to a Standard High Fat Breakfast to 29 Healthy Volunteers.

Parameter	Treatment[a] A	B	C	D	E	ANOVA p value	Multiple Comparisons[b]
AUC (ng x hr/ml)	683 (208)	688 (185)	655 (165)	662 (161)	707 (200)	0.0500	--
AUCt (ng x hr/ml)	579 (133)	604 (131)	574 (120)	592 (123)	606 (133)	0.1098	--
Cmax (ng/ml)	22.8 (4.26)	29.1 (4.82)	27.4 (4.81)	29.0 (5.43)	23.9 (4.46)	0.0001	BDCEA
Tmax (hr)	10.6 (4.06)	7.52 (2.05)	6.41 (0.983)	6.69 (1.34)	8.10 (3.07)	0.0001	AEBDC
CL/o (L/hr)	4.83 (1.63)	4.73 (1.57)	4.90 (1.36)	4.85 (1.46)	4.61 (1.48)	0.1277	--
CL/o (ml/min/kg)	1.09 (0.376)	1.07 (0.364)	1.11 (0.342)	1.09 (0.329)	1.05 (0.357)	0.1705	--
Vd/F (L)	97.3 (25.5)	86.8 (13.6)	93.3 (16.5)	88.0 (14.9)	92.4 (18.0)	0.0087	ACEDB
Vd/F (L/kg)	1.30 (0.280)	1.17 (0.158)	1.25 (0.169)	1.18 (0.124)	1.24 (0.199)	0.0155	ACEBD
λ (hr^{-1})	0.050 (0.014)	0.055 (0.014)	0.053 (0.013)	0.055 (0.012)	0.050 (0.014)	0.0001	EABCD
t½ (hr)[a]	13.9	12.6	13.1	12.6	13.9	--	--

[a] Treatment A: one 3 mg XANAX XR Tablet, one hour before meal
Treatment B: one 3 mg XANAX XR Tablet, immediately after meal
Treatment C: one 3 mg XANAX XR Tablet, one hour after meal
Treatment D: one 3 mg XANAX XR Tablet, two hours after meal
Treatment E: one 3 mg XANAX XR Tablet, fasting

[b] Multiple comparisons were made using the Waller-Duncan k-ratio t test.

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Table 7. Two One-Sided Test Analysis of AUC and Cmax Resulting from Single Oral Doses of 3 mg XANAX XR Tablets Administered at Different Times Relative to a Standard High Fat Breakfast to 29 Healthy Volunteers

Parameter	Treatment Comparison[a]	t1	t2	Pr(t>t1)	Pr(t>t2)	90% Confidence Interval
AUC	A vs E	6.2185	8.5613	0.0000	0.0000	92 - 101
AUC	B vs E	6.3646	8.4152	0.0000	0.0000	93 - 102
AUC	C vs E	4.6662	10.1136	0.0000	0.0000	88 - 97
AUC	D vs E	4.9753	9.8045	0.0000	0.0000	89 - 98
AUC	A vs D	8.1627	5.6784	0.0000	0.0000	99 - 108
AUC	B vs D	8.3088	5.5303	0.0000	0.0000	99 - 109
AUC	C vs D	6.6105	7.2286	0.0000	0.0000	94 - 104
AUC	B vs A	7.2851	6.9930	0.0000	0.0000	96 - 105
AUC	C vs A	5.5868	8.6913	0.0000	0.0000	91 - 100
AUC	B vs C	8.5447	5.1480	0.0000	0.0000	100 - 110
Cmax	A vs E	4.3150	6.8906	0.0000	0.0000	89 - 101
Cmax	B vs E	11.6568	-0.4512	0.0000	0.6736	116 - 128
Cmax	C vs E	9.6428	1.5628	0.0000	0.0605	109 - 120
Cmax	D vs E	11.4741	-0.2685	0.0000	0.6056	115 - 127
Cmax	A vs D	-0.3607	13.9575	0.6405	0.0000	74 - 84
Cmax	B vs D	6.9611	6.6157	0.0000	0.0000	96 - 105
Cmax	C vs D	4.9671	8.6297	0.0000	0.0000	90 - 100
Cmax	B vs A	12.6868	-1.9969	0.0000	0.9758	121 - 134
Cmax	C vs A	10.6728	0.0171	0.0000	0.4932	114 - 126
Cmax	B vs C	8.4378	4.4093	0.0000	0.0000	101 - 111

[a] Treatment A: one 3 mg XANAX XR Tablet, one hour before meal
Treatment B: one 3 mg XANAX XR Tablet, immediately after meal
Treatment C: one 3 mg XANAX XR Tablet, one hour after meal
Treatment D: one 3 mg XANAX XR Tablet, two hours after meal
Treatment E: one 3 mg XANAX XR Tablet, fasting

7.2.1.1 Reviewer's comment on P/2002/0017

- High fat meal when given immediately before or 2 hours before the dosing of 3mg XR tablet significantly affects the bioavailability of Xanax XR tablet by shortening tmax and increasing Cmax (on average, by 21-26%) (Table 7-1, 7-4; Fig 8 & 9). The 90% CI of test (fed)-to-reference (fasted) ratio fell outside the 0.80-1.25 goal-post for average BE assessment for the log transformed PK parameter [Cmax with 90% CI of 116-128 (M/2002/0017) and 116.16-135.87 (P/2002/0013); 115-127 (P/2002/0017] and these differences were statistically significant ($p<0.0001$)((Table 7-2, 7-3) The mean tmax was shortened from 8.1 hours (fasted) to 6.41-6.69 hours (food taken 1-2 hour prior to dosing), 7.52 hours (food taken immediately prior to dosing). The mean AUC and elimination half-lives were comparable. On the other hand, when high-fat meal was given 1 hour after the dosing of 3mg XR tablet it has no effect on the PK parameters (AUC and Cmax), but prolonged the mean tmax from 8.1 hours to 10.6 hours.
- The food-effect may be dose dependent (cross-study comparisons). When the high-fat meal was taken immediately before the dosing of 1mg XR tablet it had minimal effect on PK parameters (AUC, Cmax, tmax)(Table 7-5, 7-6; Fig 10).
- In addition, review of individual concentration-time profile for the 3mg XR tablet given with food (1hour after dosing, immediately before dosing, 1or 2 hours before dosing) indicates that in some individuals dosage form-food interaction may be quite significant (-34~+84% for Cmax and –63% to +433% for tmax) [M/2002/0017(Chou). Note: tmax effects may not be accurate since in some subjects, PK profile was flat]. Similar magnitude of % change in Cmax (+50-+75%) was observed from study [M/2000/0013 (Hossain)] when XR tablet was given immediately after a high fat meal (Table 7-1)
- Results from food-effect studies indicated that food taken immediately before the dosing of 3mg XR tablet significantly affects the bioavailability of alprazolam by increasing Cmax (an average of 21-26% with 90% CI of 116-135 which fell outside of goal post) and shortening tmax (an average of a 21-34% earlier tmax). The food effect is prolonged even when the food was taken 2 hours before the dosing. These results indicate that separating XR tablet dosing from food intake maybe warranted. Ideally, XR tablet should be taken with an empty stomach or preferably at least 1 hour before or 2 hours after a meal.
- However, since the pivotal efficacy trial was conducted with 1-10mg once daily administered at nighttime with no regard of food intake, the text associated with significant food effect on bioavailability should be incorporated in the label (Pharmacokinetics section) but not necessarily in the dosage and administration section.

Table 7-1 Range of % change in Cmax & tmax relative to the reference (3mg in fasted state, treatment E) and 90% CI of AUC &Cmax. Bold indicates outside of goal post (80-125).

Group		Treatment A	B	C	D	E (Reference)
Treatment		1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fed)	1x 3mg XR (fasted)
Meal time		1 hour after dosing	Immediately before dosing	1 hour before dosing	2 hours before dosing	Not applicable
AUC	90% CI	92-101	93-102 [87.95-104.9 (P/200/0013)]	88-97	89-98	
Cmax	90%CI	89-101	**116-128 [116.16-135.87 (P/200/0013)]**	109-120	**115-127**	
	Range of % change	-34%~+69.7% (mean -2.6%)	[-12%~+84% (mean+24.7%)]; [highest of +50-+75% (mean +26%, P/200/0013)]	-20~+78% (mean +16.8%)	-12~+67% (mean +22.8%)	0
Tmax	Range of % change	-63%~+433% (mean +55%)	-50~+100% (mean +6.32%) [(mean -34%, P/200/0013)]	-50%~+100 (mean –8%)	-50%~+100% (mean -3.7%)	0

Table 7-2; Figure 8 [protocol P/2002/0017 (Chou' review)]: Pharmacokinetics and pharmacodynamics of alprazolam relative to meal timing.

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Table 6. Mean (± standard deviation) Alprazolam Pharmacokinetic Parameters Resulting From Single Oral Doses of 3 mg XANAX XR Tablets Administered at Different Times Relative to a Standard High Fat Breakfast to 29 Healthy Volunteers.

Parameter	Treatment* A	B	C	D	E	ANOVA p value	Mu Comp
AUC (ng x hr/ml)	683 (208)	688 (185)	655 (165)	662 (161)	707 (200)	0.0500	
AUCt (ng x hr/ml)	579 (133)	604 (131)	574 (120)	592 (123)	606 (133)	0.1098	
Cmax (ng/ml)	22.8 (4.28)	29.1 (4.82)	27.4 (4.81)	29.0 (5.43)	23.9 (4.46)	0.0001	BD
Tmax (hr)	10.6 (4.06)	7.52 (2.05)	6.41 (0.983)	6.69 (1.34)	8.10 (3.07)	0.0001	AE
Cl/o (L/hr)	4.83 (1.63)	4.73 (1.57)	4.90 (1.36)	4.85 (1.46)	4.61 (1.48)	0.1277	
Cl/o (ml/min/kg)	1.09 (0.376)	1.07 (0.364)	1.11 (0.342)	1.09 (0.329)	1.05 (0.357)	0.1705	
Vd? (L)	97.3 (25.5)	86.8 (13.6)	93.3 (16.5)	88.0 (14.9)	92.4 (18.0)	0.0087	AC
Vd? (L/kg)	1.30 (0.280)	1.17 (0.158)	1.25 (0.169)	1.18 (0.124)	1.24 (0.199)	0.0155	AC
λ (hr⁻¹)	0.050 (0.014)	0.055 (0.014)	0.053 (0.013)	0.055 (0.012)	0.050 (0.014)	0.0001	EA
t½ (hr)*	13.9	12.6	13.1	12.6	13.9	–	

* Treatment A: one 3 mg XANAX XR Tablet, one hour before meal
Treatment B: one 3 mg XANAX XR Tablet, immediately after meal
Treatment C: one 3 mg XANAX XR Tablet, one hour after meal
Treatment D: one 3 mg XANAX XR Tablet, two hours after meal
Treatment E: one 3 mg XANAX XR Tablet, fasting
Multiple comparisons were made using the Waller-Duncan k-ratio t test.
Treatments connected by a line are not significantly different (p<0.05).
* Elimination half life, harmonic mean

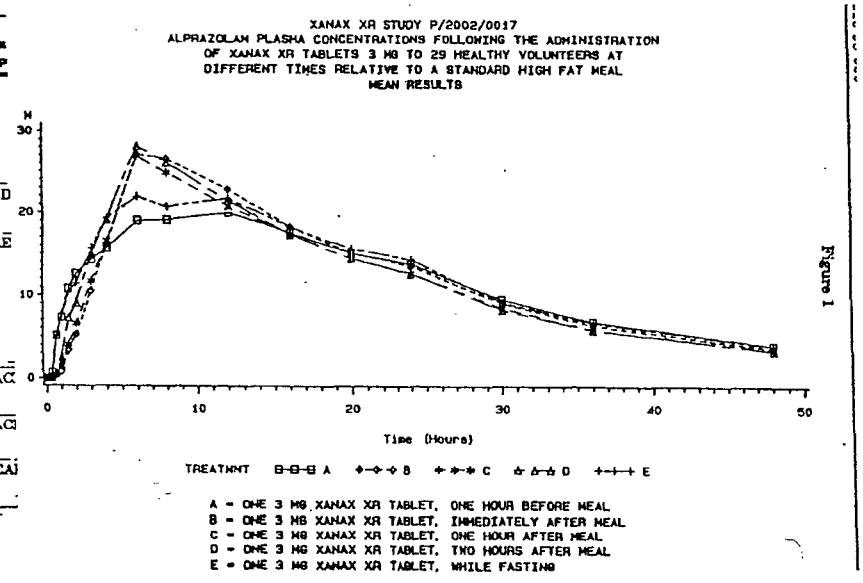


Figure 1

Table 7-3; Table 7-4 ; Figure 9: (directly excerpted from Dr. Hossain's review from protocol M/2002/0013: Effects of food on the bioavailability of XR-3mg tablets). Effects of food on the bioavailability of XR-3mg tablets.

Group	Treatment A	B	C
Treatment	1x 3mg XR tablet (fasted)	1x 3mg XR tablet (fed)	1x 3mg IR tablet (fasted)

Results: Table 15

Mean (CV, %) Alprazolam Pharmacokinetic Parameters Following Oral Administration of 1-mg ASR Tablets Administered With and Without Food and 1-mg ACT Tablets to 21 Healthy Volunteers

Parameter	Tmt. A Fasting	Tmt. B Fed	Tmt. C Fasting	ANOVA*	W-D MCT†
$AUC_{0-\infty}$ (ng·hr/mL)	229.2 (26)	212.3 (27)	217.3 (33)	NS‡	
Cmax (ng/mL)	8.2 (19)	9.2 (17)	13.4 (18)	0.0001	C B A
Tmax (hr)	7.2 (39)	7.0 (31)	1.5 (49)	0.0001	A B C
F_{rel}	1.00 (12)	0.97 (8)	1.00 (0)		
$T_{1/2}$ (hr)	14.3 (33.3)	12.4 (30.2)	13.1 (30.7)	NS	
$\bar{\lambda}$ (hr^{-1})	0.053 (30)	0.062 (34)	0.057 (34)	NS	

* Analysis of variance for latin square design, level of significance.
† Treatments sharing underhead bars are not significantly different at the 95% confidence interval
‡ No significant differences among treatments (p>0.05).

ure 19 - Mean Alprazolam Plasma Concentration-Time Profiles

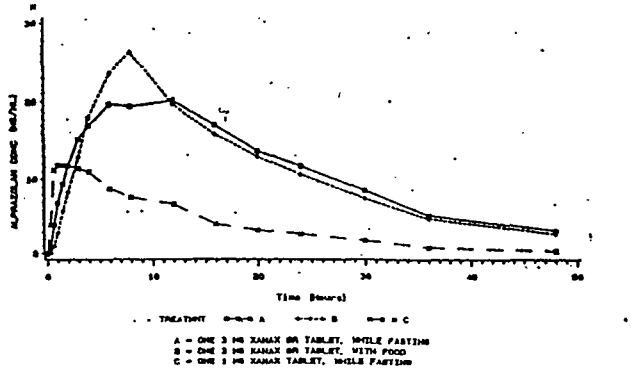


Table 32

90% Confidence Interval Analysis (Two One-Sided Test Procedure) For Selected Alprazolam Pharmacokinetic Parameters. Parameters Corrected For Mean Assayed Tablet Lot Potency.

Parameter	Treatment	MSE	90% C.I.	Result	Power*
$AUC_{0-\infty}$ (ngxhr/mL)	B vs A	9057.45	87.95-104.18	Pass	99
Cmax (ng/mL)	B vs A	16.05	116.66-135.87	Fail	93
AUC_0 (ngxhr/mL)*	A vs C	739.39	98.36-113.10	Pass	99
	B vs C	739.39	94.19-108.93	Pass	99
$Cmax_0$ (ng/mL)*	A vs C	7.57	42.40-63.30	Fail	88
	B vs C	7.57	56.34-77.24	Fail	88
Tmax (hr)	B vs A	6.81	52.76-78.38	Fail	73
	A vs C	6.81	455.28-589.05	Fail	7.6
	B vs C	6.81	275.48-409.25	Fail	7.6

* Power to detect a 20% difference between treatment and reference means at an α level of 0.05.
* Normalized to a 1.0 mg dose.

Table 7-5; Table 7-6; Figure 10 : (directly excerpted from Dr. Hossain's review from protocol M/2000/0275: Effects of food on the bioavailability of XR-1mg tablets).

Group	Treatment A	B	C
Treatment	1x 1mg XR tablet (fasted)	1x 1mg XR tablet (fed)	1x 1mg IR tablet (fasted)

Results:

Table 15

Mean (CV, %) Alprazolam Pharmacokinetic Parameters Following Oral Administration of 1-mg ASR Tablets Administered With and Without Food and 1-mg ACT Tablets to 21 Healthy Volunteers

Parameter	Tmt. A Fasting	Tmt. B Fed	Tmt. C Fasting	ANOVA*	W-D MCT†
$AUC_{0-\infty}$ (ngxhr/mL)	229.2 (26)	212.3 (27)	217.3 (33)	NS*	
Cmax (ng/mL)	8.2 (10)	9.2 (17)	13.4 (18)	0.0001	C B A
Tmax (hr)	7.2 (39)	7.0 (31)	1.5 (49)	0.0001	A B C
F_{rel}	1.00 (12)	0.97 (8)	1.00 (0)		
$T_{1/2}$ (hr)	14.3 (33.3)	12.4 (30.2)	13.1 (30.7)	NS	
β (hr^{-1})	0.053 (30)	0.062 (34)	0.057 (34)	NS	

* Analysis of variance for latin square design, level of significance.
† Treatments sharing underhead bars are not significantly different at the 95% confidence interval
* No significant differences among treatments ($p > 0.05$).

Figure 8

am Plasma Concentrations Following Oral Administration of Tablets 1 mg and XANAX Tablets 1 mg to 21 Healthy Volunteers - Mean Results For All Subjects

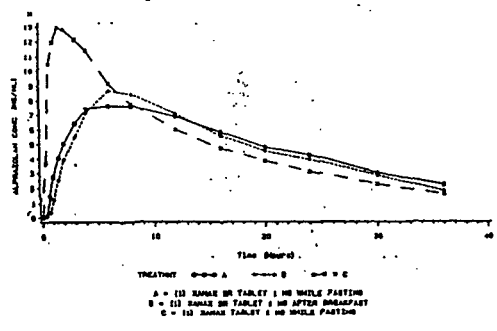


Table 16

90% C. I. Analysis (Two One-Sided Test Procedure) For Selected Alprazolam Pharmacokinetic Parameters. Pharmacokinetic Parameters Corrected Based On The Mean Potency Of The Lots.

Parameter	Treatment	MSE	90% C.I.	Result	Power*
AUC (ng x hr/mL)	A vs C	521.295	100.01-110.94	Pass	99.99
	B vs C	521.295	92.23-103.17	Pass	99.99
	B vs A	521.295	87.44-97.81	Pass	99.99
Cmax (ng/mL)	A vs C	1.325	56.72-65.66	Fail	99.99
	B vs C	1.325	64.19-73.13	Fail	99.99
	B vs A	1.325	104.89-119.5	Pass	99.34

* Power to detect a 20% difference between treatment and reference means at an α level of 0.05.

Conclusions: The bioavailability of alprazolam from the 1-mg sustained release tablet is not statistically significantly affected by food.

7.2.2 Literature-based Drug-drug interaction studies

No drug-drug interaction study was performed with the XR tablet to evaluate the PK or safety/efficacy. The sponsor proposed to use labeling language of marketed Xanax IR (Revised June 2000) as template and incorporated the new literature-based drug-drug interaction information between alprazolam IR and CYP3A4 inhibitors (ketoconazole, itraconazole, and erythromycin), and CYP3A4 inducer (carbamazepine), respectively. This reviewer agrees with Hossain's conclusion that the factor such as drug-drug interaction that may affect the PK of alprazolam after the administration of IR tablets would not be expected to change with the administration of XR tablets since the metabolism of alprazolam is not affected by the absorption rate (IR versus XR) and alprazolam is extensively metabolized with minimal unchanged drug found in the urine.

A total of five articles containing additional DDI information were submitted and reviewed by this reviewer. One additional article regarding DDI with grapefruit, which was submitted to Pharm/Tox section, was also reviewed by this reviewer. Results are summarized in table below (Table 7-7).

Table 7-7

CYP3A4 inhibitor					
	Study design	formulation/dose	Results	Reviewer's comment	Reference
ketoconazole	Double-blind, 5-way cross-over, single dose, placebo-controlled study, 7 healthy male volunteers, non-smoker (21-44yrs)	Ketoconazole (200mg bid) + 1.0mg alprazolam IR or 0.25mg triazolam	Ketoconazole significantly reduced clearance(27 Vs 86ml/min; p<0.002), prolonged the apparent elimination t1/2 (59 Vs 15 hours; p<0.03), and increased the AUC (237±43 Vs 944±277ng.hr/ml) of alprazolam. The Cmax was slightly increased (16.1 Vs 14.7ng/ml)	The dose of Xanax used in this study is relatively low compared to the therapeutic dose of Xanax (5-6mg/day).	Greenblatt DJ et al 1998
itraconazole	Randomized, double-blind, crossover, placebo control, 6 weeks washout. 5 male volunteers (Japanese, mean 31.7 yrs old)	Itraconazole: single 200mg dose for 6 days. Xanax: single 0.8mg oral dose on day 4.	Itraconazole significantly increased AUC (252±47 Vs 671±205ng.hr/ml), decreased the apparent oral clearance (0.89±0.21 Vs 0.35±0.10 ml/min/kg), and prolonged the elimination t1/2(15.7±4.1 Vs 40.3±13.5 hours) of alprazolam. The psychomotor function variables (sleepiness from UKU side effect rating scale) differed significantly.	The dose of Xanax used in this study is relatively low compared to the therapeutic dose of Xanax (5-6mg/day).	Yasui N et al 1998
erythromycin	Randomized, double-blind, crossover, placebo control, 6	Erythromycin: 400mg (tid) for 10 days. Xanax: single 0.8mg oral dose on	Erythromycin significantly increased AUC (299±52 Vs 566±161ng.hr/ml), decreased the apparent oral clearance (1.02±0.31	The dose of Xanax used in this study is relatively low compared to the therapeutic dose of Xanax (5-6mg/day).	Yasui N et al 1996

	weeks washout. 12 male volunteers (Japanese, 25-41 yrs old)	day 8.	oral clearance (1.02±0.31 Vs 0.41±0.12 ml/min/kg), and prolonged the elimination t1/2(16.0±4.5 Vs 40.3±14.4 hours) of alprazolam. The psychomotor function variables (visual analog scale, UKU side effect rating scale) did not differ significantly.		
grapefruit juice(GFJ)	study 1: randomized two-way crossover study, with an interval of 4 wks. Eight males average age 31.1 yrs (6 smokers(≥ 10 cigarettes/d)	Xanax IR Study 1: 0.8mg single dose on 8th day of 10 days GFJ administration (healthy volunteers) Study 2: 0.4mg, 0.8mg or 1.2mg bid for 2-10 days (patients with anxiety disorders including panic disorders) GFJ: regular strength 200ml (Dole, Snow Brand Milk Products Co., Ltd, Tokyo, Japan)	Study 1: No difference in Cmax(water Vs GFJ: 12.4±2.3 Vs 13.3±3.1ng/ml, AUC(243±48 Vs 272±62ng h/ml) and t1/2 (15.5±4.6 Vs 18.9±3.6h). In six smokers, a significant increase in AUC (245±56 to 288±62ng h/ml $p<0.05$), and prolonged t1/2 (14.1±to 19.5±2.9 hrs $p<0.05$) Study 2: No significant difference in plasma alprazolam concentrations (before and during co-administration of GFJ and 1 wk after its discontinuation: 14.6±9.9, 16.9±11.8 and 13.4±10.4 ng/ml, respectively)	*The dose of Xanax used in this study is relatively low compared to the therapeutic dose of Xanax (5-6mg/day). * The results from these 2 studies may not be truly reflective of potential DDI between GFJ and alprazolam. The sponsor did not propose to include GFJ in the label. This reviewer does not intend to propose additional labeling language in this regard: 6/8 volunteers were heavy smokers and smoking is a confounding factor since it showed a potential effect on PK of alprazolam (↑clearance by 100% in smokers) (section 4.6.2; Hossain et at)	Yasui N et al 2000

CYP3A4 inducer

	Study design	dose	Results	Reviewer's comment	Reference
Carbamezepine	double-blind, randomized, placebo-controlled, crossover study with 2 phases. 7 male volunteers	carbamazepine 300mg/d x 10 days, alprazolam IR (0.8mg) on day 8.	*Carbamazepine significantly increased the apparent oral clearance (0.90±0.21 Vs 2.13±0.54 ml/min/kg) and shortened the elimination t1/2 (17.1±4.9 Vs 7.7 ±1.7 h), with no significant effect on the Cmax (11.7±1.5 Vs 13.3±3.5 ng/ml) and tmax (1.6 ±0.7 Vs 1.0 ±0.9 h). Carbamazepine cause an average of 60% decrease in mean plasma alprazolam concentration	* The carbamazepine dose used is fairly low (maximum daily dose is 1000-1200mg/day in divided doses).	Furukori H et al 1998

			at 0.5 h ($p<0.001$) *The majority of the psychomotor function parameters (Visual analog scale, UKU side effect rating scale)during the carbamazepine treatment were not significantly different from those of placebo treatment.		
St John's Wort	7 healthy subjects (3F+4M), 24-32 yrs old, Caucasian. Phase I: 3 subjects Phase II: 4 subjects	Phase I: dextromethorphan 30mg +alprazolam IR 1mg; Phase II: St John's Wort [(300mg tid x 4 days); Solaray, Park City, UT)] dextromethorphan 30mg (day 3)+alprazolam IR 2mg (day 3).	PK parameters (Phase I Vs Phase II)* Mean Tmax : 3.1 Vs 1.8 hrs Mean Cmax: 12.4 Vs 14.2 Mean t1/2: 7.6 Vs 5.8hrs Mean AUC: 179 Vs 105 ng/ml/h * all p-values (paired two-tailed student's t-test) were>0.05	*The authors concluded that there is lack of significant PK changes and the 3-day pre-treatment may be too short. *The sponsor did not propose to include St John's Wort in the label. *This reviewer does not intend to propose additional labeling language in this regard for the following reasons: (a) small sample size, no control group (b) different doses (1mg Vs 2mg) were given in different phases but the authors did not mention any dose-normalization of PK parameters (Cmax & AUC).	Markowitz JS et al 2000

7.2.3 In vitro release methods and specifications

Proposed by the sponsor: The sponsor proposed in the original [redacted] and is again proposing for the drug release assay the pH 6.0 phosphate buffer medium using USP apparatus I and different specifications for 4 different strengths.

	0.5 mg	1 mg	2 mg	3 mg
1 hour	[redacted]			
4 hours				
8 hours				
16 hours				

Recommended by the Agency under previously NDA submission [redacted] The following interim dissolution method and specification recommended by the Agency and agreed between the Agency and the sponsor before the NDA was [redacted]

Note: There was extensive discussion between Agency and the sponsor in this regard before Xanax XR NDA (NDA 21,434) was [redacted] At the time, both Agency and the sponsor agreed on the following drug release method and specification (Hossain's reviews dated 11/29/1993, 03/06/1995).

USP apparatus I (rotating basket) at 100 rpm in 500ml deionized medium at 37±0.5°C

Sampling Time	0.5, 1.0, 2.0, and 3.0 mg ASR Tablets
1 hr	NMT [redacted]
4 hr	[redacted] %
8 hr	[redacted] %
12 hr	NLT [redacted]

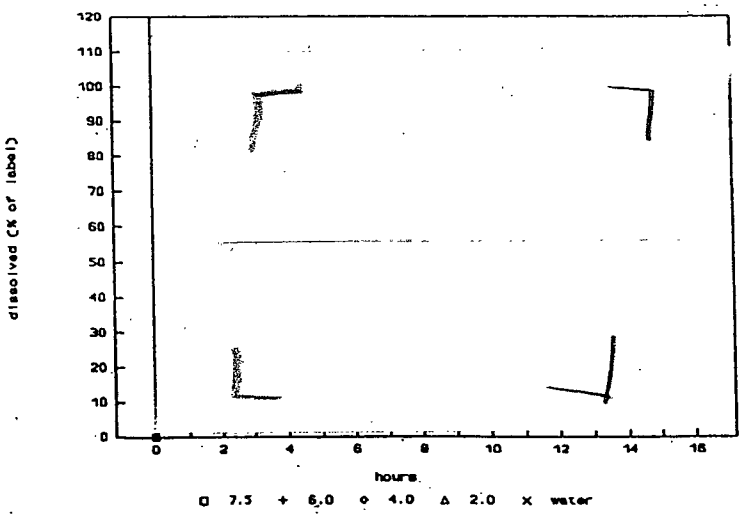
Current submission: At Agency's request, the sponsor provided some justification for choosing the proposed dissolution specifications and method over the one that was agreed upon between the Agency and the sponsor under [redacted] However, there was no new information in this regard submitted since the sponsor [redacted]

7.2.3.1 Comments from current reviewer

- This reviewer agrees with the sponsor's proposed dissolution medium (pH 6.0 phosphate butter). This is supported by 2 reasons described below: (1) The dissolution profiles are similar for Xanax XR 1mg in 4 different media (water, pH 4.0, 6.0 and 7.5 phosphate buffer)(Figure 11). (2) Choosing pH 6.0 phosphate buffer over water as dissolution medium may provide some benefits due to the lack of buffer capacity in water .

Figure 11

Figure II.G-2 Dissolution profiles for XANAX XR 1 mg Lot 85,317 with dissolution media of water, pH 2.0, pH 4.0, pH 6.0 and pH 7.5.



- Based on the guidance published after the sponsor [redacted], this reviewer agrees with sponsor's proposed method, medium (pH 6.0 phosphate buffer) and individual specifications.
- Ideally, one common specification should be used for all 4 different strengths. However, in this specific case, where a strength-dependent drug release phenomenon exists, dissolution specs has to be widened to accommodate all 4 strengths. To justify this widening, an established in-vitro and in-vivo correlation (IVIVC) is required*. IVIVC was unsuccessful for XR tablet (4.7.2.1, page 33). Therefore, the dissolution specifications will be used as QC measures and different acceptance criteria for different strengths are being set.
  *The guidance published in September 1997 "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations".
- This reviewer has evaluated sponsor's proposed dissolution specs at any time point against dissolution profiles from following batches used to establish BA/BE & efficacy, and support [redacted] manufacturing site change [Table 7-8. Details of individual dissolution profile are attached below (Table 7-9, 7-10, and 7-11)].
  (a) Batches used in the pivotal PK/BE & efficacy studies manufactured at US site (old site, undebossed) as primary data.
  (b) Batches manufactured at the Arecibo, Puerto Rico (new site, undebossed) used in the BE study (data submitted [redacted], to support the manufacturing site change as primary data. The dissolution profile from the biobatches for this BE study was not available.
  (c) Dissolution profiles from commercial final formulation (new site, 2-sided debossed) were used as supportive data.
  (d) Dissolution profiles from final formulation (new site, undebossed, data is not attached in this review).
  (e) The review chemists (Drs. Thomas Oliver & Lorenzo Rocca) were also asked to evaluate the sponsor's proposed dissolution specifications against the stability data.

We agree with the sponsor proposed specifications. Final dissolution method and specification:
USP apparatus I, 100rpm, 37°C, volume 500ml, pH 6.0 buffer

	0.5 mg	1 mg	2 mg	3 mg
1 hour				
4 hours				
8 hours				
16 hours				

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Table 7-8

Old site Kalamazoo, Michigan (no debossing)				New site: Arecibo, Puerto Rico. submitted undebossed: one-sided debossing with "strength"*	
Strength	Study type	study protocol	lot #	lot#	**comment
0.5mg	R2002/0001	BA of XR 0.5mg and 1mg tablet	35,562	36636 from 64991	
				64995	
				64996	
1mg	M/2000/0369	pivotal efficacy	35,477	64998***	
	R2002/0001	BA of XR 0.5mg and 1mg tablet	35,563		
	M/2000/0253	dose proportionality and BE in different strengths	23,436		
	M/2000/0352	BE in different strengths	87,317		
2mg	M/2000/003	dose proportionality and BE in different strengths	35,695	64997	
	M/2000/0352	BE in different strengths	24,092		
3mg	M/2000/0352	BE in different strengths	24,095	36635 from 64992	
	R/2002/0002	PK of 6mg qd dosing	35,697	36677 from 64999	
	R/2002/0010	PK of 3mg bid dosing	35,796	36678 from 65000	
				65001	

* Final production batch will be manufactured at new site with 2-sided debossing (with strength on one side and "X" on the other side). Dissolution data comparing debossed and undebossed tablets from all 4 strengths will be discussed separately in section 7.2.4, page 65.

** Several of the dissolution data from the batches manufactured at the new sites were also submitted under current NDA. However, the sponsor did not specify the manufacturing site. This reviewer used information submitted under previous NDA and summarized in the table above.

***Dr Hossain had requested the sponsor to submit the dissolution data from the biobatches of 3 mg XR tablets used to demonstrate BE between 2 sites (P/2002/0018) using the dissolution method and specification Agency recommended. In response to the Agency's request, the sponsor submitted dissolution data for all 4 strengths from production-scale batches manufactured at the Arecibo, Puerto Rico (new site) and lot 35,796 [made in old site and used in another BE study (R/2002/0010)].

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Table 7-11 New site (debossed, commercial production)

Table 5
Single Tablet Dissolution Results for XANAX XR (TA2984) - Debossed

Lot Number	Time (hrs)	% of label dissolved HI	LO	AVG*	Std Dev†	Individual Tablet Data (% of label dissolved)
0.5 mg						
65,565	1			20	2	
	2			33	1	
	4			54	2	
	6			71	2	
	8			85	2	
	12			103	2	
	16			111	2	
1 mg						
65,568	1			18	3	
	2			29	3	
	4			48	3	
	6			65	2	
	8			79	2	
	12			98	2	
	16			106	2	
2 mg						
65,571	1			14	4	
	2			24	3	
	4			40	3	
	6			54	2	
	8			67	2	
	12			88	4	
	16			102	3	
3 mg						
65,574	1			12	3	
	2			21	4	
	4			37	2	
	6			51	2	
	8			63	2	
	12			83	4	
	16			96	4	

* Average calculated from raw data.
† Standard deviation calculated from individual tablet data reported in table.

7.2.4 Dissolution profiles to support the debossing issues

After Xanax XR was submitted (12/26/01) under NDA21,434 for review, the sponsor submitted (05/10/02) a request for teleconference along with three questions regarding stability and debossing issues for discussion. The sponsor proposed that XANAX XR Tablets will be debossed with a stylized "X" on one side and tablet strength on the other. This represents a change from the debossing associated with stability lots. Most of the stability lots reported in NDA 21-434 were [redacted] with no debossing and all of the confirmatory stability lots will be [redacted] with no debossing. It should be noted that neither clinical nor biopharmaceutical studies were conducted using to-be-marketed debossed tablet.

Sponsor: The sponsor argued that although addition of debossing has the potential of substantially influencing drug release from modified- release dosage forms, the addition of the proposed debossed markings to XANAX XR Tablets is not expected to alter the drug release characteristics of these products. This conclusion is based on scientific studies conducted during product development that examined the effect on drug release of tablet surface area and tablet volume variations associated with

different tablet shapes. Pharmacia & Upjohn proposes that addition of the proposed debossed markings is well within the surface area and tablet volume variations studied.

Following comment was conveyed to the sponsor during teleconference:
The sponsor is requested to submit dissolution profile comparisons between debossed and non-debossed tablets using the selected dissolution method for all strengths (0.5, 1, 2, and 3 mg) of Xanax XR. The sponsor was informed that while dissolution was comparable for tablets with different shapes, the experiments conducted do not evaluate the effect of changes ——— . Since the Belgian tablets are not debossed in the same manner as the proposed U.S. tablets and since we have no information on the effect of different ——— on release rate, it is prudent to compare dissolution profiles of debossed and non-debossed tablets.

Note: The sponsor indicated in the teleconference that they anticipate the debossed tablets will be manufactured ——— and they agreed to submit the requested information as soon as they become available. Later, on September 13, 2002, the sponsor submitted the comparisons of debossed with undebossed tablets from 1 full scale lot of each strength. The stability data were also submitted and reviewed by Chemist, Lorenzo Rocca, Ph.D.

7.2.4.1 Reviewer's Comments for debossing issues

- The dissolution profiles are similar between the debossed (commercial production) and undebossed tablets using the selected dissolution method for all 4 strengths (0.5, 1, 2, and 3 mg) of Xanax XR. An f2 test performed by the sponsor indicated all f2 values are greater than 80 for 0.5mg, 1mg, 2mg and 3mg strengths. The results summarized below indicated that the debossing does not affect the drug release from the tablets of all 4 strengths (**Table 7-12**). Individual drug release profiles are attached below (page 69).

Table 7-12 Dissolution profile comparison for 3 lower strengths XR tablets (0.5, 1, and 2 mg) manufactured at the new and old sites

pH 6.0 phosphate buffer											
	0.5mg		1mg			2mg			3mg		
Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2	Lot # (debossed)	Lot # (un-debossed)	f2
65565	65517	87	65568	65520	81	65571	65523	85	65574	65526	86
	65518	84		65521	81		65524	100		65527	80
	65519	87		65522	96		65525	84		65528	67

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7.4 Pharmacometrics review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 21,434	**Submission Dates:** December 26, 2001, January 4, 2002, March 28, 2002 May 2, 2002, May 21, 2002.
Drug Name:	[redacted]
Formulation:	Extended Release Tablets (0.5, 1, 2, 3 mg)
Dosage:	starting dose: 0.5 mg to 1 mg once daily; maintenance dose: [redacted]
Applicant:	Pharmacia & Upjohn Company
Consult:	To evaluate the acceptability of BID dosing regimen
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Background:

XANAX immediate release (IR) tablets were approved (NDA 18,276) for the treatment of panic disorder. The present submission includes the information related to a sustained release formulation of alprazolam (alprazolam XR tablets).

The sponsor indicated that the effectiveness of alprazolam IR tablets in the treatment of panic disorder has been previously established. The results from study #4432 demonstrated that patient response, based on the reduction of major panic attacks, was related to steady-state alprazolam plasma concentrations based on data at doses of 2 and 6 mg/day of alprazolam IR tablets. However, it should be noted that the sponsor indicated in the clinical summary section that results from analyses of #4432 and another trial #4412 (a short-term study with IR tablet) did not establish a minimum effective alprazolam dose, concentration or window of effective doses or levels. The pivotal effectiveness trial (#4452) for alprazolam XR tablet was carried out with a once daily regimen. The sponsor proposed once-daily (QD) [redacted] regimens for the XR tablet for the treatment of [redacted]

The sponsor justified BID dosing with XR product (only QD regimen was tested in the pivotal clinical trial) based on the population PK/PD of Xanax IR in the panic disorder patient population and PK data observed from the QD and BID regimens of XR tablets. These results along with the single effectiveness clinical trial (#4452) have been submitted to support the approval of the Xanax XR (once-[redacted] dosing in panic disorders). At the pre-NDA meeting, the FDA has informed the sponsor that t[redacted]a for XR formulation will be acceptable if plasma profiles of XR formulation given BID are completely bracketed by XR (QD) and IR (approved dosing regimen).

PK/PD relationship for XR product administered BID has not been evaluated. The PD endpoints in the PK/PD trials are psychomotor performance (i.e. EEG and DSST), which are different from the endpoints (panic attacks) measured in the effectiveness trial. Additionally, the study population in the PK/PD trials with XR product consists of only healthy volunteers.

Objectives:

To assess whether BID regimen for the XR tablet can be recommended for the treatment of panic disorder.

Methods:

Pharmacokinetic performance of IR and XR formulations at steady state was compared in two studies (protocols R/2002/0002 and M/2002/0010).
Study protocol R/2002/0002 was designed as an open-label, single and multiple dose two-way crossover study.
The two treatments were

A: Two 3 mg XANAX XR tablets
B: One 1 mg and one 0.5 mg (total dose of 1.5 mg) XANAX IR tablets.

XR tablets were administered once a day in the morning (6 mg QD) and IR tablets were administered four times a day (1.5 mg QID). In addition, initial doses of both treatments were studied to confirm that single dose pharmacokinetics are in fact predictive of steady state results. Blood samples were collected up to 36 hours after the single dose (intensive sampling scheme), at trough plasma concentrations on day 6 and day 7, and up to 48 hours after the last dose.
Study protocol M/2002/0010 was also designed as an open-label, single and multiple dose two-way crossover study.
The two treatments were

A: Two 3 mg XANAX XR tablets
B: One 1 mg and one 0.5 mg (total does of 1.5 mg) XANAX IR tablets.

XR tablets were administered twice a day every 12 hours (6 mg BID) and IR tablets were administered four times a day (1.5 mg QID).

Blood sampling scheme was similar to the study protocol R/2002/0002 with a few additional samples obtained on day 6.
In both studies the drug was administered to a population of healthy volunteers with similar demographic characteristics:

Study	N	Age, years (mean)	Weight, kg	Male%
R/2002/0002	20	19-54 (32)	61-102	100
M/2002/0010	17	20-47 (32)	52-95	48

Analytical:

Plasma concentration data for alprazolam, α-hydroxyalprazolam, and 4-hydroxyalprazolam were assayed using a normal phase HPLC method. The interday coefficient of variation for alprazolam at the low end [redacted] of the standard curve was 2.5% and at the upper end [redacted] was 3.2%. The intraday coefficient of variation for α-hydroxyalprazolam, and 4-

hydroxyalprazolam was 1.9% and 2.2% at 1 ng/mL and at 100 ng/mL it was 2.6% and 2.5% respectively.

Data Analysis:

Plasma concentration data for alprazolam, α-hydroxyalprazolam, and 4-hydroxyalprazolam were analyzed using non-compartmental methods. The comparison of the treatments were performed using a mixed effect ANOVA model with group, period, and treatment as fixed effects and subject within group as a random effect. Comparisons between the treatments were also made using confidence interval analysis (two one-sided t-test). All statistical analyses were performed using SAS.

Results:

The data from 20 subjects (study M2002/0002) and from 17 subjects (study R2002/0010) were available for the data analysis.
The Cmin data for the last day of dosing were compared for all treatments in these studies. Results of this comparison are shown in Table 1. Mean (SD) Cmin alprazolam plasma concentrations for IR treatments were similar: 47.02 (17.42) ng/mL, with the range of [redacted] (study 0002) and 55.28 (25.12) ng/mL, with the range of [redacted] /mL (study 0010). Mean Cmin alprazolam plasma concentrations for XR treatment with BID dosing (study 0010) was 57.5 (25.73) ng/mL with the range [redacted]. This value is similar to Cmin measured for IR tablets and 60% higher than when alprazolam was dosed QD (study 0002, 36.35 (17.7) ng/mL, [redacted]. Therefore, after the administration of Xanax at the dose of 6 mg per day, Cmin alprazolam plasma concentrations obtained in the treatment with XR tablets BID overlap Cmin alprazolam plasma concentrations obtained in the treatment with IR tablets QID and are higher than the same values obtained for XR tablets administered QD.

Alprazolam IR tablets administered at doses of 6 mg/day are generally effective in the treatment of panic disorder. Alprazolam XR tablets, administered once daily have been shown to be effective in the treatment of panic disorder. The effectiveness of alprazolam IR at doses of 2 mg and 6 mg per day was previously proved to be associated with its plasma concentrations at steady state (sponsor's study report 9112-87-005). In this report, the PK/PD model linked alprazolam plasma concentrations after the last dose and probability of attaining a specific response (decrease in number of total panic attacks). The logistic regression model was applied, and equation derived from the logistic analysis was as follows:

$$P_{major} = \frac{\exp(-2.07 + 0.075 \cdot C_i)}{1 + \exp(-2.07 + 0.075 \cdot C_i) + \exp(0.13 + 0.047 \cdot C_i)}$$

where P_{major} is a probability of being classified a major responder and C_i are alprazolam plasma concentrations after the last dose of drug.

This equation was used by the reviewer to calculate the probability of attaining a major response after the last dose treatment in studies 0002 and 0010 (Table 1). Trough alprazolam plasma concentrations were used as C_i values.

Table 1. Comparison of the observed plasma concentrations measured at trough and calculated effects of alprazolam in studies 0002 and 0010.

Study	**0002**		**0010**	
Regimen	**IR 1.5 mg QID**	**XR 6 mg QD**	**IR 1.5 mg QID**	**XR 3 mg BID**
Cmin, ng/mL				
Mean (SD)	47.02 (17.42)	36.35 (17.7)	55.28 (25.12)	57.5 (25.73)
Range	—	—	—	—
Probability of major response to alprazolam concentrations at Cmin, (%)				
Mean	27.38	20.92	32.84	34.36
Range	12.53-65.03	10.29-59.15	19.93-80.38	16.98-81.25

The pharmacokinetics of alprazolam IR at steady state was described with the population pharmacokinetic model. In the studies 0002 and 0010 trough plasma concentrations for the IR formulations were measured at approximately the same time interval (4-6 hours after the dose).

The probability of attaining the major response calculated for the mean trough alprazolam plasma concentration after administration of XR tablets BID was similar with the results for IR tablet obtained in the same study 0010. This probability was higher than the results from the study 0002 for either IR or XR tablets (QD). The ranges of the calculated response for each treatment in these studies overlap.

COMMENTS

1. The range of Cmin alprazolam plasma concentrations for the XR BID treatment is between the Cmin measured for IR (QID) and XR (QD). The range of calculated response at the trough plasma alprazolam level for all three treatments in both studies 0002 and 0010 overlap as well.

2. The PK/PD model used for the calculation of the probability of decrease in panic attacks did not consider the time course of effect. Therefore, it cannot be used to predict the pharmacodynamic effect for different dosing regimens (IR Vs XR tablets).

3. The summary data on the effectiveness and safety of the comparable regimens needs to be carefully considered (see Comments to the MO).

4. The sponsor's conclusions on safety and effectiveness of [redacted] BID treatment regimen for alprazolam XR tablets should be considered with respect to the onset of the drug effect, possibility of self upward titration performed by the patients, drug withdrawal effect and compliance.

COMMENTS TO THE MEDICAL OFFICER:

1. Although the pharmacokinetic profiles for alprazolam obtained after the administration of IR and XR formulations are similar, the conclusion of whether the time course of effect (desired/undesired) needs to be considered.

2. In the clinical summary, the sponsor stated that during the long-term study of IR tablets, no statistical significant differences were found between the maintenance group and the group with 50% dose reduction suggesting that after the achievement of the therapeutic effect, the alprazolam IR dose may be reduced. The sponsor studied the effect of slow and fast tapering of the dose alprazolam IR or XR. Only one study (M/2000/0271) directly compared the discontinuation of IR Vs XR regimens in a 6 weeks study. A greater percent of patients in XR group (76%) had difficulty in tapering in comparison with IR group (67%). At the end of taper, the alprazolam treated patients had greater change in total panic attacks in XR (+3.86) Vs IR (+2.82) Vs placebo (+0.33) groups.

3. In placebo-controlled studies, the premature treatment discontinuation in treatment phase was more associated with XR group of patients (28%) than with IR group (10%). The table below shows the details of the reasons for premature treatment discontinuation. The main reason for that was the occurrence of medical events (16.6%, XR and 4.3% IR groups).

	Alp XR[a] N=506		Alp IR[a] N=70		Placebo[a] N=324	
Reason for Premature Discontinuation[a]	n	%	n	%	n	%
Total Premature Discontinuations	**141**	**27.87**	**7**	**10.00**	**101**	**31.17**
Improvement	1	0.20	0	0.00	0	0.00
Lack of efficacy	13	2.57	1	1.43	45	13.89
Medical Events	84	16.60	3	4.29	12	3.70
Other	10	1.98	1	1.43	4	1.23
Patient Decision/Lost to Follow-up	24	4.74	0	0.00	34	10.49
Protocol Violator	9	1.78	2	2.86	6	1.85

a Includes Studies: M/2000/0271 [26], M/2000/0369 [25], M/2002/0002 [27], and M/2002/0003 [28]
N = Number of ITT patients with a recorded disposition
n = Number of patients who prematurely discontinued
% = Percentage based on number of ITT patients with a recorded disposition
Data Source: ISS Source Table 1.04.01, Listing 1.04.01

4. In the same studies, in the discontinuation phase, the results were opposite: XR formulation performed slightly better than IR formulation (25.3% Vs 29.0% of total discontinuation cases).

5. The results of the data analysis of adverse events were controversial as well. Table below shows that in the treatment phase about 50% of patients in XR group had at least one treatment associated adverse event (9% in IR group). However, serious adverse events were 4 times more frequent in IR group (16%) Vs XR group (4%). The similar tendency was demonstrated for the adverse events in the discontinuation phase.

Placebo-Controlled Studies: Treatment Phase	ALP XR	ALP IR	Placebo
Pts with at least 1 adverse event	489 (92.09)	68 (97.14)	290 (83.09)
Pts with at least 1 Related TES	268 (50.47)	6 (8.57)	73 (20.92)
Pts with TES causing study medication termination	91 (17.14)	6 (8.57)	27 (7.74)
Pts with Serious TES	19 (3.58)	11 (15.71)	18 (5.16)
Pts with Any Serious Event leading to discontinuation	12 (2.26)	5 (7.14)	6 (1.72)
Placebo-Controlled Studies: Discontinuation Phase	**ALP XR**	**ALP IR**	**Placebo**
Pts with at least 1 discontinuation event	348 (82.46)	56 (90.32)	180 (68.97)
Pts with at least 1 Related DES	84 (19.91)	4 (6.45)	20 (7.66)
Pts with DES causing study medication termination	35 (8.29)	5 (8.06)	2 (0.77)
Pts with Serious DES	18 (4.27)	14 (22.58)	6 (2.30)
Pts with Any Serious Event leading to discontinuation	3 (0.71)	2 (3.23)	1 (0.38)

Pts = Patients, TES = treatment-emergent symptom (adverse event), DES =discontinuation-emergent symptom(adverse event)
Source Tables ISS

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the reports of the Studies R/2002/0002 and M/2002/0010. Although the pharmacokinetic profiles as well as the calculated pharmacodynamic effects for alprazolam obtained after the administration of IR and XR formulation are similar, the conclusion of the same efficacy and safety of both formulations may be controversial.
The reasons for the substitution of once daily administration of Xanax XR tablets with twice daily administration of XR tablets are not persuasive.

/S/

Date_____

Elena Mishina, Ph. D.
Pharmacometrics Specialist

/S/

Joga Gobburu, Ph.D.
Pharmacometrics Team Leader

cc list: NDA 21,434, Mehta M, Marroum P , Mishina E, HFD 120

BIOPHARM

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Number of Pages Redacted 25

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(not releasable,

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Study Reports/Publications

1. [redacted] Absence of effect of food on alprazolam absorption from sustained release tablets (Protocol M/2000/0275). Upjohn Technical Report 7215-91-018, 26 June 1991.	Item 6/Vol 16/ Pg 129
2. [redacted] Steady-state pharmacokinetics and pharmacodynamics of alprazolam after administration of [redacted]® tablets and XANAX® tablets: I. XANAX SR tablets administered once a day (Protocol R/2002/0002). Upjohn Technical Report 7215-91-019, 23 July 1991.	Item 6/Vol 17/ Pg 1
3. Wright CE, Chambers JH. Steady-state pharmacokinectics and phrmacodynamics of alprazolam after administration of [redacted] tablets and XANAX® tablets: II. XANAX SR tablets administered twice a day (Protocol P/2002/0010). Upjohn Technical Report 7215-91-022, 25 July 1991.	Item 6/Vol 20/ Pg 1
4. [redacted] Influence of food on the bioavailability of alprazolam from 3 mg [redacted] tablets (Protocol P/2002/0013). Upjohn Technical Report 7215-91-024. 26 July 1991.	Item 6/Vol 24/ Pg 1
5. Wright CE, Sisson TA, Fleishaker JC, Antal EJ. Pharmacokinetics and pharmacodynamics of alprazolam in healthy volunteers following single oral doses of 2 to 10 mg of XANAX SR® tablets (Protocol R/2002/0003). Upjohn Technical Report 7215-91-014, 11 June 1991. *Publication reference:* Wright CE, Sisson TL, Fleishaker JC, Antal EJ. Alprazolam pharmacokinetics and psychomotor performance; concentration-effect relationship. J Clin Pharmacol 1997;37:321-9.	Item 6/Vol 30/ Pg 1
6. Greenblatt DJ, Wright CE, vonMoltke LL, Harmatz JS, Ehrenberg BL, Harrel LM, et al. Ketoconazole inhibition of triazolam and alprazolam clearance: Differential kinetic and dynamic consequences. Clin Pharmacol Ther 1998; 64:237-47.	Item 6/Vol 25/ Pg 58
7. Yasui N. Kondo T. Otani K, Furukori H, Kaneko S, Ohkubo T, et al. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. Psychopharmacology 1998;139:269-73.	Item 6/Vol 25 /Pg 43
8. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. J Clin Psychopharmacol 1995;15:399-408.	Item 6/Vol 25/ Pg 48
9. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. Eur J Clin Pharmacol 1994;46:35-9.	Item 6/Vol 25/ Pg 75
10. Yasui N, Otani K, Kaneko S, Ohkubo T, Osanai T, Sugawara K, et al. A kinetic and dynamic study of oral alprazolam with and without erthromycin in humans: in vivo evidence for the involvement of CYP3A4 in alprazolam metabolism. Clin Pharmacol Ther 1996;59:514-9.	Item 6/Vol 25/ Pg 69
11. Furukori H, Otani K, Yasui N, Kondo T, Kaneko S, Shimoyama R, et al. Effect of carbamazepine on the single oral dose pharmacokinetics of alprazolam. Neuropsychopharm 1998;18:364-9.	Item 6/Vol 25/ Pg 106
12. [redacted] Effect of Alprazolam Release Rate from Immediate and Extended Release Tablets on Abuse Liability in Man (Protocol P/2002/0008). Upjohn Technical Report 7215-94-021, July 21, 1994.	Item 6/Vol 42/ Pg 1

7.6 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-434	Brand Name	XANAX XR (extended release tablets)
OCPB Division (I, II, III)	I (HFD-860)	Generic Name	alprazolam
Medical Division	HFD-120	Drug Class	Triazolobenzodiazepine related to the benzodiazepine
OCPB Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.	Indication(s)	Panic disorder with or without agoraphobia
OCPB Team Leader	Ramana, Uppoor. Ph.D.	Dosage Form	Tablets (0.5, 1, 2, 3mg)
Date of Submission	12/26/01	Dosing Regimen	Proposed: starting dose: 0.5mg to 1mg once daily; maintenance dose:between [redacted] nd 6mg per day; daily dose can be given as qd [redacted] Maximum: 10mg/day
Estimated Due Date of OCPB Review	07/30/02	Route of Administration	po
Division Due Date	8/30/02	Sponsor	Pharmacia & Upjohn Company
PDUFA Due Date	10/25/02	Priority Classification	s

Background

- Xanax (alprazolam) is marketed as an immediate release (IR) oral dosage form indicated for the treatment of anxiety and panic disorders with or without agoraphobia. [redacted], the sponsor (Upjohn Co) submitted an NDA (under [redacted] for Xanax XR (extended-release) tablets for panic disorders with or without agoraphobia based on bio-studies and one positive clinical study. At that time, sponsors were required to have two controlled clinical trials that evaluated the efficacy of a new formulation of the marketed drug substance. The sponsor [redacted] . However, the recent FDA Guidance document published in 1998 entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" indicates that the effectiveness of a new dosage form may be extrapolated from efficacy data from another dosage form when well-defined pharmacokinetic/pharmacodynamic relationships exist. In addition, if the relationship between blood concentration and response is not well understood, a single additional efficacy study can be sufficient to provide evidence of effectiveness.
- Dr. Mohammad Hossain reviewed this NDA and recommended that the NDA is approvable from OCPB's perspective (11/29/1993, 8/5/1993). Following comments were sent to the sponsor: modify dissolution method and specifications, update labeling regarding DDIs by performing literature search , in-vitro metabolism study, explore PK/PD relationship in target population and include covariates analysis, single versus bid dosing in assessing PK/PD relationship. Furthermore, an agreement was reached for setting a common dissolution specification using water as medium for all strengths of Xanax XR. DSI inspection was satisfactory for 3 studies [BE of XR 3mg bid and IR(P/2002/0010); food study (P/2002/0013), BE of 1, 2, and 3mg XR(M/2000/0352)].
- In a pre-NDA meeting (6/15/2001) for Xanax XR under IND#23,179, the sponsor was requested to submit one positive efficacy clinical trial along with PK characterization of Xanax XR, and its safety data, as a basis for approval. In addition, following OCPB comments from Dr. Gerald Fetterly were conveyed to the sponsor: full data analysis of PK/PD studies; relative alprazolam concentrations from bid of XR relative to those from qd of XR and qid of IR products; updated labeling from literature regarding ADME, DDIs, in-vitro metabolism, electronic submission, development of IVIVC.
- The sponsor is resubmitting Xanax XR under current NDA. A total of 23 studies are submitted. Eighteen of them were previously reviewed by Dr. Hossain under [redacted] The sponsor is seeking approval of XR products based on the BE studies, one positive clinical trial of XR product, and PK/PD relationship established with IR product (report #4432, under NDA18,276/S017 dated 8/5/1987, which was previously reviewed by clinical and statistical division).

- Following are the 5 new studies with XR product: PK of XR product relative to meal timing, (N=1), abuse liability (N=1), PK/PD in healthy volunteers [N=3: proof of concept (N=1), data from other 2 studies were neither provided nor analyzed by the sponsor]

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed previously (will be reviewed by current reviewer)	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	fasting/SD	3	3(0)	
fasting / non-fasting multiple dose:	fasting/md	1	1(0)	
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2/3:		8	0(0)	XR pivotal efficacy trial (M/2002/0369) [#4452] was previously submitted to

				However, efficacy was not reviewed at that time. PD measures: panic attack changed from the baseline submitted in clinical section (QD, XR, 1-10mg X 6 wks). Note: Blood levels were measured in 2 efficacy trials (M/2002/0369 & M/200/0271). However, the sponsor did not provide PK data or PK & PK/PD analysis because of the following reasons: (1) the concerns in quality of lab measures, (2) Pop PD of IR had been evaluated, (3) Pop PK of XR had been described in the literature.
PK/PD:				
Phase 1 and/or 2, proof of concept:		7	4 (0) (*M/2002/0044, *M/2002/0037)	XR [(double-blind, in healthy volunteers; PD measures: psychomotor performance (EEG and/or DSST)] [*2 new studies: sponsor neither provided PK/PD measures nor data analysis, only safety was discussed]. (Dosing regimen studied include: sd, 2-10mg qd; md,1-6mg, qd; md, 3mg, bid; md, 0.5mg, bid; md, bid with different doses)
Phase 3 clinical trial:				
Population Analyses -				• report (#4432, IR in panic-disorder population, submitted under NDA18,276/S017 dated 8/8/5/1987, which was previously reviewed by clinical and statistical division). [pop PK/PD: clearance of active treatment groups (2 or 6mg/d) between response subpopulations (none, moderate, major) based on response index derived from the change in number of panic attacks between baseline and last treatment)
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:	x	1	1(0)	
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:	X	2	2(0)	(IR as ref)
Bioequivalence studies -	X			
traditional design; single(SD) / multi (MD) dose:	X (SD)	13 (11SD, 2MD)	13(0)	
replicate design; single / multi dose:				
Food-drug interaction studies:	x	3	2(1)	(assess the PK of XR product relative to meal timing)
Dissolution:	x	5	5(0)	(M/2300/235 (7215-89-001) maybe a typo of M/2000/235 in HPK ref section)
(IVIVC):	x	1	0(0)	
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	x	1	1(0)	
Pediatric development plan				
Literature References	x	48	7	including PK/PD for IR (NDA18,276), pop pk of IR & XR (sd & md)
Total Number of Studies	x	23 different studies (total # of studies may exceed this # because some studies serve multiple purposes)	18 different studies (1 study +literature regarding DDI+in-vitro dissolution method & specification+ dissolution profiles to support manufacturing site change and debossing issue were reviewed by current reviewer)	• 18/23 were previously reviewed by Dr. Hossain, comments were sent to the sponsor before the NDA. • Note: blood levels were measured in 2 efficacy trials (M/2002/0369 & M/200/0271). However, the sponsor did not provide PK data or PK & PK/PD analysis because of the following reasons: (1) the concerns in quality of lab measures, (2) Pop PD of IR had been evaluated, (3) Pop PK of XR had been described.

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	Pharmacometrics consult on pop PK/PD of IR (#4432, previously reviewed by clinical & statistical divisions), and PK/PD of XR (pending discussion of clinical relevance of PD measures), if necessary.
Comments sent to firm ?		You are requested to submit the following: Justification and full report for choosing the proposed dissolution specifications and method over the one that was

		agreed upon between the Agency and you in this regard under Full report of in-vitro in-vivo correlation (IVIVC) development with at least two release rates and demonstration of IVIVC predictability. If there are any questions, please contact the Agency. Following FDA guidance for electronic submission, submit electronic data related to PK and dissolution data for the IVIVC studies.
QBR questions (key issues to be considered)		1. From the Agency's and sponsor's perspective, what changes have been made since the sponsor Focus will be on how the sponsor responded to the comments from the agency, and on new information submitted by the sponsor since last agency's review of Xanax XR. 2. In order to support bid dosing of XR, does the plasma concentration for bid dosing with XR fall between the qd dosing with XR and qid dosing with IR? 3. Was population PK and PK/PD of Xanax been properly analyzed? (#4432, IR) 4. Is there a well-defined PK/PD relationship for alprazolam administered as Xanax XR? 5. What are the PK characteristics of the Xanax XR relative to meal timing? 6. Was the IVIVC properly developed and does it demonstrate satisfactory predictability? 7. Are the proposed dissolution specifications and method appropriate to distinguish suboptimal batches? 8. Were the to-be-marketed XR formulations identical to the formulations submitted under
Other comments or information not included above		Pharmacometrics (PM) consult may be submitted. Information regarding the PK/PD of IR and XR products provided in this submission will be discussed between the PM scientist and reviewer after the filing meeting to determine whether a detailed PM review is necessary since the PD measures of XR product are not the same as the clinical endpoints. Additional information from the sponsor may be needed in future.
Primary reviewer Signature and Date		Wen-Hwei Chou, Pharm.D., Ph.D.
Secondary reviewer Signature and Date		Ramana Uppoor, Ph.D.

CC: NDA 21,434 Alprazolam extended release (Xanax XR), HFD-850 (Lee), HFD-120(CSO), HFD-860 (Mehta, Sahajwalla, Uppoor, Gobburu, Sekar, Chou), CDR

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wen-Hwei Chou
10/16/02 02:40:36 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/16/02 02:48:59 PM
BIOPHARMACEUTICS
Joga to sign for Pharmacometrics review

Jogarao Gobburu
10/16/02 03:55:03 PM
BIOPHARMACEUTICS
Dr. Mishina is on leave, hence the Gobburu is signing on her behalf as well.

COMPLETED JAN 13 2003 JAN 10 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults

From: Wen-Hwei Chou, Pharm.D., Ph.D.			To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE:	IND No: NA	NDA No: 21,434 (amendment #16)	DATE OF DOCUMENT	11/20/2002
NAME OF DRUG/ Formulation & strength /Route of Administration/Indication Xanax XR (alprazolam extended release tablets, 0.5, 1, 2, & 3 mg)/po/Panic disorder with or without agoraphobia **Related IND/NDA**: NA	PRIORITY CONSIDERATION Standard		Date of informal/Formal Consult:	12/03/2002

NAME OF THE SPONSOR: Pharmacia & Upjohn

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

___PRE-IND	___DISSOLUTION/IN-VITRO RELEASE	___FINAL PRINTED LABELING
___ANIMAL to HUMAN SCALING	___BIOAVAILABILITY STUDIES	___LABELING REVISION
___IN-VITRO METABOLISM	___IN-VIVO WAIVER REQUEST	___CORRESPONDENCE
___PROTOCOL (New IND)	___SUPAC RELATED	___DRUG ADVERTISING
___PHASE II PROTOCOL	___CMC RELATED	___ADVERSE REACTION REPORT
___PHASE III PROTOCOL	___PROGRESS REPORT	___ANNUAL REPORTS
___DOSING REGIMEN CONSULT	___SCIENTIFIC INVESTIGATIONS	___FAX SUBMISSION
___PK/PD- POPPK ISSUES	___MEETING PACKAGE (PRE-ADVISORY MEETING)	X OTHER *(SPECIFY BELOW)*:
___ PHASE IV RELATED		**Complete response to approvable letter dated 10/25/2002**

REVIEW ACTION

___NAI (No action indicated) ___E-mail comments to: ___Medical___Chemist_Pharm-Tox ___Micro___ Pharmacometrics___Others (Check as appropriate and attach e-mail)	___Oral communication with Name: [ ] ___Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	___Formal Review/Memo (attached) X See comments below ___See submission cover letter ___OTHER *(SPECIFY BELOW)*:

REVIEW COMMENT(S)

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Attachment 3: Brief review

Comparison of alprazolam plasma levels in normal Asian and Caucasian male volunteers.
Lin KM et al Psychopharmacology (1988) 96:365-69

Study design & Method: A total of 42 healthy male volunteer subjects were studied. They were equally divided in the following three groups: Caucasians (C, n=14), American-born Asians [ABA, n=14: Chinese (n=3), Filipino (n=5), Japanese n=6)], and foreign-born Asians (FBA, n=14: Chinese (n=10), Filipino (n=3), Japanese n=1)]. After a 12-hour fasting, at 7AM, alprazolam (0.5mg) was administered either as an oral tablet or slow IV injection (1mg/mg, over 1-min period). Two testing sessions were separated by at least a 2-week interval. Blood was collected for PK analysis at following time points: prior to the dose (-1.0 h, -0.5h, 0.0h), and at 10, 20, and 40 min, and 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 8.0, 12.0, 24.0, and 36.0 h after the dose.

Data analysis: Plasma alprazolam concentration-time data were fitted to the sum of 2 or 3 exponentials using CSSTRIP. Analysis of variance was used to compare PK variables (AUC, Cmax, Cl, elimination rate constant, Vd, tmax). Body surface area was used in these comparisons as a covariate.

Results:

- There are significant differences between the Asian and Caucasians in AUC, Cmax, Cl after oral and iv testing. Following oral administration: Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asian compared to Caucasians (Fig 2, table 2).

- After factoring in body surface area as a covariate, significant ethnic differences continued to exist for oral AUC, CL and t1/2, but not in any of the IV parameters.
- When the two Asian groups were pooled together and compared with the Caucasians, the above cross-ethnic differences become more prominent.

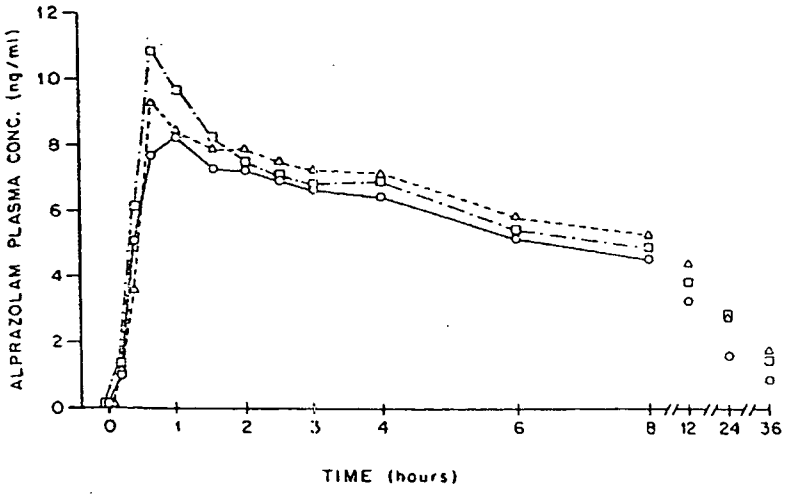

Fig. 2. Mean plasma alprazolam concentrations after a 0.5 mg single dose of alprazolam as an oral tablet in Caucasian (*C*), American-born Asian (*ABA*) and foreign-born Asian (*FBA*) subjects. o—o C ($n=14$); Δ-----Δ ABA ($n=14$); □-·-□ FBA ($n=14$)

Table 2. Comparison of pharmacokinetic parameters after intravenous alprazolam administration in three study groups

	Caucasians (C)	American-born Asians (ABA)	Foreign-born Asians (FBA)	ANOVA ($df=2,39$)		ANCOVA (with body surface area as covariate) ($df=2,39$)	
				F	*P*	*F*	*P*
AUC (ngxh/ml)	165 ±39.2*	213 ±63.7	210 ±68.7	3.00*	<0.1 (=0.0609)	1.04	NS
C_{max} (ng/ml)	12.6 ± 2.04	15.2 ± 2.78	14.4 ± 2.87	3.45*	<0.05	0.61	NS
CL (l/h)	3.17± 0.66	2.52± 0.69	2.65± 1.00	3.04*	<0.1 (=0.0591)	1.06	NS
$t^1/_2$ (h)	13.4 ± 3.42	16.0 ± 5.36	17.8 ± 6.80	1.46	NS	1.26	NS
T_{max} (min)	10.9 ± 2.6	12.2 ± 4.1	16.6 ±21.3	0.55	NS	0.55	NS
V_d area (l)	59.2 ±10.50	54.2 ± 8.90	60.0 ±10.4	1.64	NS	1.57	NS

Significant differences with paired comparisons: * ABA vs C

* Mean±SD

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