CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-190

Clinical Pharmacology and Biopharmaceutics Review

MEMORANDUM

COMPLETED JUN 13 2000

To: **Division File NDA 21-190**

From: **Hong Zhao / Raman Baweja** 6/12/2000 6/12/2000 JUN 12

Date: **June 12, 2000**

Re: **Dissolution Specification for BuSpar® (Buspirone HCl) Capsules**

A meeting was held between OCPB review team (Dr. Baweja and Dr. Zhao) and Chemistry review team (Dr. Seevers and Dr. Rocca) on June 6, 2000 to discuss dissolution specification issue for NDA 21-190, BuSpar® (Buspirone HCl) Capsules.

The OCPB review by Dr. Parmalee recommended dissolution specification to be Q not less than — based on dissolution data from biobatches. Dr. Rocca presents the stability data which indicate that the capsule drug product would fail the — — specification after 3 months of storage and for some production batches would fail the specification even at the zero time of storage.

Based on the fact that the biobatches of capsule formulation and tablet formulation, which showed comparable bioavailability, have the same — and similar dissolution performance — **the dissolution specification for BuSpar® capsule product is recommended as not less than 80% in 30 minutes,** which is the same as what the firm proposes and is also the same as the specification for the corresponding tablet dosage form (NDA 18-731).

Please convey this recommendation to the sponsor.

CC: NDA 21-190
HFD-120/Rseevers
HFD-120/LRocca
HFD-120/AHomonnay
HFD-860/MMehta
HFD-860/RBaweja
HFD-860/HZhao

Clinical Pharmacology/Biopharmaceutics Review

AHO

NDA: 21-190
Buspar (buspirone HCl) 5 mg, 7.5 mg, 10 mg, and 15 mg capsules
Bristol-Myers Squibb
Submission Date: September 23, 1999

Reviewer: Thomas A. Parmelee, Pharm.D.

Type of Submission: NDA for a new capsule formulation of buspirone HCl

SYNOPSIS

Buspar (buspirone HCl) is an antianxiety drug that is chemically and pharmacologically different than the benzodiazepines, barbiturates, and other sedative/anxiolytic agents. Buspirone HCl is currently marketed (under NDA 18-731) as 5mg and 10mg Buspar tablets and 15mg Dividose tablets. The sponsor has submitted an NDA for the approval of a new capsule formulation of buspirone HCl.

Section 6 (Human Pharmacokinetics and Bioavailability) of the current NDA submission contains three (3) clinical pharmacology/biopharmaceutics studies. The comparative studies used the highest strength (15mg) buspirone capsule planned for marketing, and the currently marketed buspirone Dividose tablets (15mg) as the reference. According to the Orange Book, the 15mg tablet was the clinically studied strength used to show safety and efficacy for approval of the tablet formulation of Buspar.

The sponsor has adequately investigated the comparative pharmacokinetics of Buspar Capsules 15mg using the currently approved Buspar Dividose tablet 15mg as the reference. The comparative oral bioavailability of buspirone between the capsule and tablet formulations has been examined using the stable isotope technique. The sponsor has also submitted the results of a preliminary study (CN101-128) that confirm that an isotope effect is not observed in the pharmacokinetics of stable labeled [13C, 15N2]buspirone compared to unlabeled compound. Finally, the sponsor has examined the comparative food effects on the capsule and tablet formulations of buspirone HCl. For all studies, pharmacokinetic analysis was performed on both the parent buspirone compound and its active metabolite, 1-pyrimidinylpiperazine (1-PP). The sponsor has referenced the FDA Guidance for Industry entitled: "Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing". This guidance is attached to this review as **Appendix 1.** Upon review of the data from the three BE studies, the dissolution data for all proposed capsule strengths, and the proposed labeling, the Office of Clinical Pharmacology and Biopharmaceutics finds the NDA to be approvable. Study summaries are attached to this review as **Appendix 2.**

RECOMMENDATION

The sponsor's NDA 21-190 meets the biopharmaceutics requirements and is acceptable provided the comments regarding product dissolution and labeling are adequately addressed by the sponsor.

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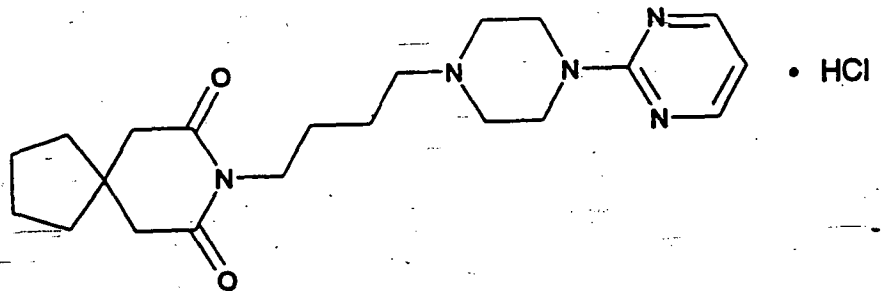
BACKGROUND

Buspirone hydrochloride is a white crystalline, water-soluble compound with a molecular weight of 422.0. Chemically, buspirone HCl is 8-[4-[4-(2-pyrimidinyl)-1-piper-azinyl]butyl]-8-azaspirol[4.5]decane-7,9-dione monohydrochloride. The structural formula is:



Buspirone is currently supplied as tablets (Buspar) for oral administration containing 5, 10, or 15mg buspirone HCl (equivalent to 4.6, 9.1, and 13.7mg of buspirone free base, respectively). It is indicated for the treatment of generalized anxiety disorder. The sponsor wishes to market a new capsule formulation of buspirone HCl. The sponsor believes that a new capsule formulation of buspirone HCl may improve patient compliance as well as offer a more convenient alternative for dosage administration.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS

I. BIOAVAILABILITY

a) Bioequivalence

The Buspar 15mg capsules were found to be bioequivalent to Buspar 15mg tablets (Study CN101-126).

b) Food Effects

Study CN101-127 examined the relative effects of a high fat meal on the rate and extent of absorption of buspirone from the tablet and capsule formulation, as well as from the capsule contents emptied and mixed with applesauce. A high fat meal increased the Cmax of buspirone from the capsule formulation approximately 17% compared to the fasted state. The AUC (inf) of buspirone under fed conditions increased approximately 2-fold relative to the fasted state for the capsule formulation. For the active metabolite 1-PP from the capsule formulation, the Cmax decreased 32% under fed conditions while the AUC (inf) was not significantly affected.

The capsule administered under fed conditions was also compared to the reference tablet administered under fed conditions. There was a 20% decrease in Cmax of buspirone when the capsule was administered under fed conditions compared to the reference tablet administered under fed condition. AUC (inf) was not affected. There was no significant difference in 1-PP pharmacokinetics between the capsule formulation and tablet formulation under fed conditions.

The sponsor also examined the effects of opening the contents of the buspirone capsule and mixing with applesauce and administering under fed conditions. Relative to the administration of intact capsule under fed conditions, the pharmacokinetic parameters for the open capsule contents Cmax and AUC (inf) increased by 19% and 12%, respectively. There was no significant effect on 1-PP levels between the intact capsule administered under fed conditions relative to the capsule contents emptied and mixed with applesauce under fed conditions.

Finally, the comparison was made between the intact capsule formulation administered under fasting conditions relative to the capsule contents mixed with applesauce and administered under fed conditions. Relative to the fasting state, the capsule contents under fed conditions resulted in increases of 40% and 100% for the parameters Cmax and AUC (inf), respectively. The Cmax for 1-PP decreased 34% for the capsule contents while the AUC (inf) did not differ significantly between the two treatments.

SUMMARY OF DRUG PRODUCT

II. FORMULATIONS

According to the sponsor, the qualitative and quantitative composition of Buspar Capsules is exactly the same as the currently approved and marketed Buspar Tablets (NDA 18-731). The formulations for each capsule strength are shown in **Appendix 3** and are compositionally proportional between strengths. Buspar Capsules 5, 7.5, 10, and 15mg are prepared from —— that is filled into capsules of the appropriate weight. Only the net weight of the different strength capsules will vary. No changes in the source or manufacturing process of the bulk substance are proposed for the capsule buspirone formulation compared to the tablet formulation.

III. DISSOLUTION

The sponsor has submitted dissolution profiles from twelve (12) individual units of both product (capsule and tablet) formulations and of all strengths to be marketed/currently marketed. For the 15mg capsules and tablets, data from biobatches has been submitted. This information is attached as **Appendix 3.** The sponsor proposes the following:

Method- USP Apparatus 2 (paddle), 50 rpm, 500 mL 0.01 N HCl at 37°C

Q spec- Q not less than 80% in 30 minutes

The specification proposed by the sponsor is the same as the currently approved USP specification for Buspar Tablets. Based on the data and dissolution profiles submitted by the sponsor, the Office of Clinical Pharmacology and Biopharmaceutics recommends that the specification be amended to ***Q not less than*** —— using the above mentioned method, apparatus, and medium.

IV. ASSAY

Concentrations of buspirone and its active metabolite, 1-pyrimidinylpiperazine (1-PP), were measured in human plasma using —— method with —— Overall, the assay methodology and validation were found to be acceptable.

V. REQUEST FOR WAIVER

The sponsor has requested a waiver, as described in 21 CFR 320.22, for submitting evidence demonstrating the bioequivalence of Buspar (buspirone HCl) 5mg, 7.5mg, and 10mg capsules. The bioequivalence studies submitted to this NDA were performed on the highest strength (15mg) capsule intended for marketing. The sponsor states that the Buspar capsules 5mg, 7.5mg , and 10mg are prepared from —— with the only difference in capsule strengths being the filled capsule weights. The capsule formulations are compositionally proportional between strengths. The sponsor has compared the average dissolution profiles for the 5, 10, and 15mg strength capsules to the Buspar 5, 10, and 15mg strength tablets manufactured at the same facility. The 15mg tablet batch used for dissolution testing was the same as the batch used in the bio-studies CN101-126 and CN101-127. Similarity factors (f2) were calculated for each strength capsule compared to the reference strength tablets. Similarity factors (f2) were greater than 50 in each of the comparisons. Please refer to **Appendix 3** for capsule composition, dissolution data and profiles.

GENERAL COMMENTS (for the Clinical Division)

1) The proposed dissolution specification of Q not less than 80% in 30 minutes is not acceptable based on the dissolution profiles submitted to the Office of Clinical Pharmacology and Biopharmaceutics. The capsule is rapidly dissolving (—— ——, and the dissolution profiles show a plateau is reached within — minutes. OCPB recommends the following dissolution methodology and specification:

Method- USP Apparatus 2 (paddle), 50 rpm, 500 mL of 0.01 N HCl at 37°C
Spec- Q not less than ——

2) The request for waiver for bioequivalence testing on the 5, 7.5, and 10mg strength capsules is granted because bioequivalency has been shown between the capsule and tablet at the highest strength of 15mg, and based on the proportional similarity of qualitative and quantitative composition between capsule strengths. Also, similar dissolution profiles have been shown for each capsule strength.

LABELING COMMENTS

Appendix 4 contains the currently proposed sponsor labeling with proposed revisions. The final product labeling for Buspar capsules should resemble the currently approved labeling for Buspar tablets with the following recommended additions:

1) Under the Clinical Pharmacology Section of the Labeling:

The effects a high-fat meal on the bioavailability of Buspar Capsules have been studied in 40 healthy subjects who were given a single-dose of 30-mg buspirone with and without food. With food, the area under the plasma concentration-time curve (AUC) and peak plasma concentration (Cmax) of buspirone increased by 84% and 17%, respectively. The Cmax —— —— 1-pyrimidinylpiperazine (1-PP) decreased 33% when buspirone was administered with food, while the AUC did not differ significantly.

When the capsule was opened and its contents administered in 1 oz of applesauce following a meal, the AUC and Cmax of buspirone increased by 12% and 19%, respectively, compared to the intact capsule following a meal. 1-PP levels did not differ between treatments.

When the capsule was opened and its contents administered in 1 oz of applesauce following a meal, the AUC and Cmax of buspirone increased by —— respectively, compared to the intact capsule

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2) **For the new Buspar labeling for Capsules, the sponsor should keep the statement regarding the effect of food on the Tablets intact. This paragraph is:**

3) Under Drug Interaction Section of the Labeling (see **Appendix 5**):

Diltiazem and Verapamil: **In a study in 9 healthy volunteers, co-administration of Buspar**

RECOMMENDATIONS

NDA 21-190 meets the Office of Clinical Pharmacology and Biopharmaceutics requirements and is approvable provided the dissolution specifications and product labeling are amended as recommended above.

/S/

Thomas A. Parmelee, Pharm.D. 12/17/99

RD/FT by R. Baweja, Ph.D. /S/ 12/17/99.

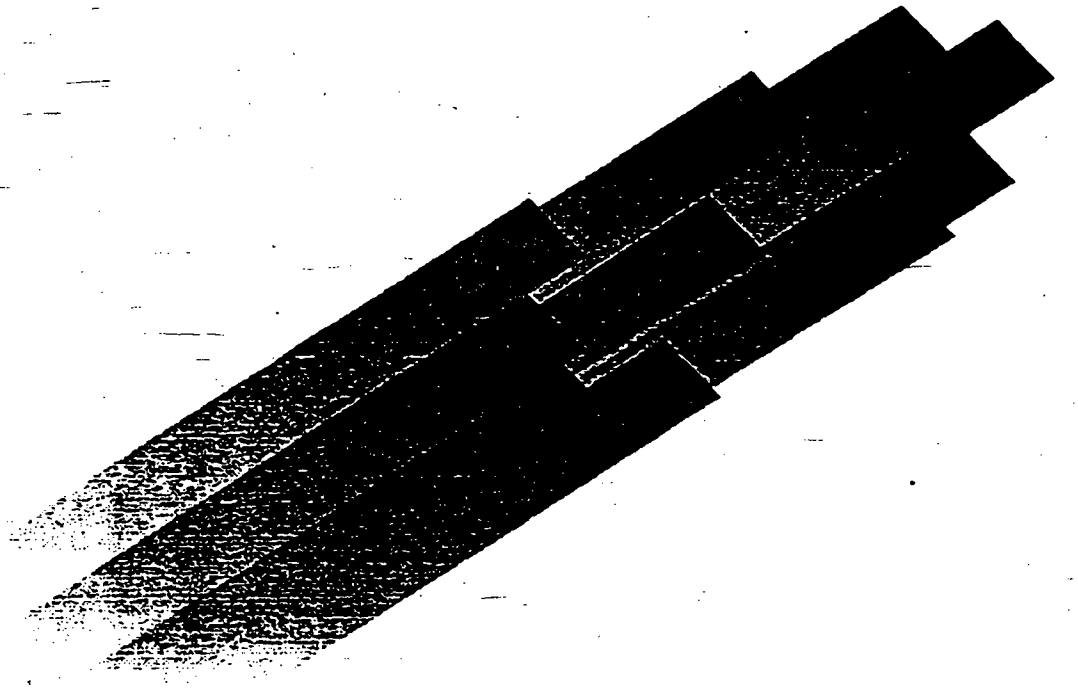
OCPB briefing held: December 16, 1999
(Attendees: Mehul Mehta, Arzu Selen, Raman Baweja, and Tom Parmelee)

CC: NDA 21-190, HFD-120, HFD-860 (Mehta, Baweja, Parmelee), CDER document room: Attn. BIOPHARM- CDR

APPENDIX 1

Guidance for Industry

Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro DissolutionTesting



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 1998
BP 4, Rev. 1

Guidance for Industry

Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 1998
BP 4, Rev. 1

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GUIDANCE FOR INDUSTRY[1]

Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing

I. INTRODUCTION

This is revision 1 of the guidance for industry on in vivo bioequivalence and in vitro dissolution testing for buspirone hydrohloride tablets. The guidance has been revised to reflect the recent availability of buspirone hydrochloride tablets in 15 milligram (mg) dosage forms. Bioequivalence is tested using the highest available dosage of the reference listed drug. The guidance also notes the nonlinearity of buspirone at multiple-dosing.

A. Clinical Usage/Pharmacology

Buspirone hydrochloride is an antianxiety agent (1, 2). Clinically it is effective in the management of anxiety disorders or short-term relief of symptoms of anxiety. Buspirone has no anticonvulsant or muscle relaxant activity and has little sedative effect. It does not substantially affect psychomotor function (3, 4). There is no evidence that the drug causes either physical or psychological dependence (5). The mechanism of action of buspirone is not known. Some in vitro preclinical studies indicate that buspirone has high affinity for serotonin (5-HT_{1A}) receptors, and moderate affinity for brain D_2 receptors (5-9).

For the management of anxiety disorders, the usual initial adult dosage of buspirone is 10 to 15 milligrams (mg) daily, usually in two or three divided doses. Dosage is increased as

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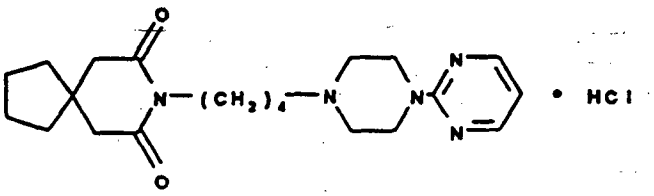
[1] This guidance has been prepared by the Biopharmaceutical Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on buspirone hydrochloride tablets in vivo bioequivalence and in vitro dissolution testing. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573.

necessary in increments of 5 mg daily to achieve an optimal therapeutic response. The maximum daily dose should not exceed 60 mg per day (5).

Buspirone is currently marketed by Bristol-Myers Squibb Company under the trade name Buspar in scored oral tablets of 5 mg, 10 mg, and 15 mg.

B. Chemistry

Buspirone hydrochloride is a white crystalline powder, soluble in water, with a molecular weight of 422. The chemical structure of buspirone is shown below:



C. Pharmacokinetics

Buspirone is rapidly and almost completely absorbed from the gastrointestinal (GI) tract. The drug undergoes extensive first-pass metabolism, with about 4 percent of a dose reaching the systemic circulation unchanged following oral administration (10,11). Following oral administration of a single dose of 20 mg in healthy volunteers, peak plasma buspirone concentrations of 1 to 6 nanograms (ng)/mL have been observed to occur within 40 to 90 minutes (5,12). Plasma concentrations of unchanged buspirone are low and exhibit substantial interindividual variation with oral administration of the drug (13). Approximately 95 percent of buspirone is bound to plasma proteins (14).

Buspirone is rapidly metabolized by oxidation to produce several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (10,15). Because of rapid metabolism, less than 1 percent of the parent drug is excreted unchanged in the urine (10). The pharmacologically active metabolite has about 20 to 25 percent of anxiolytic activity of buspirone. In humans, blood concentrations of the active metabolite (1-PP) remain low even after chronic administration of buspirone. The contribution of 1-PP to the pharmacologic and/or toxic effect thus remains to be fully elucidated.

The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is reported to be two to three hours (5). Buspirone exhibits linear kinetics following administration of single 10 to 40 mg doses (16). At higher doses given as multiple dosing, a nonlinear kinetic also was observed. However, it is unknown at what dose the nonlinearity starts. Although food increases the bioavailability of buspirone by decreasing first pass metabolism, the total amount of drug (changed and unchanged) in plasma is not affected (17,18).

II. IN VIVO BIOEQUIVALENCE STUDIES [2]

A. Product Information

1. FDA-designated reference product: BuSpar (Bristol-Myers Squibb) 15-mg tablets.

2. Batch size: The test batch or lot should be manufactured under production conditions and be of a size at least 10 percent that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5 percent.

B. Types of Studies Recommended

1. A single-dose, randomized, fasting, two-treatment crossover study under fasting conditions comparing equal doses of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence, crossover, limited-food-effects study comparing equal doses of the test and reference products when administered immediately following a standard breakfast.

C. Recommended Protocol for Conducting a Single-Dose Bioequivalence Study under Fasting Conditions

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given in equal doses.

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[2] The sponsoring firm is advised that an investigational new drug application may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1).

Design: A single-dose, randomized, two-period, two-treatment, two-sequence crossover study using a sufficient number of subjects to ensure adequate statistical results and with one week washout period between phases I and II, or a single-dose, randomized, fasting, two-treatment, four-period, four-sequence replicate design crossover study in fasting subjects with one week washout period between phases of dosing. Equal numbers of subjects should be randomly assigned to the dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles, and curriculum vitae of the medical, scientific, and analytical directors.

Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. Subjects should be healthy volunteers, 18 to 50 years in age, and within 10 percent of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study subjects before they are accepted into the studies.[3]

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose (2 x 15 mg tablets) of the test or reference product with 240 mL of water.

Restrictions: Study participants should observe the following restrictions:

1. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

2. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

3. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

[3]Please refer to 21 CFR 50.

4. Subjects should take no prescription medications beginning two weeks and no over-the counter medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: Venous blood samples should be collected predose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 7.0, 8.0, 12, and 24 hours postdose. Plasma should be separated promptly and immediately frozen until assayed. Following a washout period of at least one week, subjects should begin the second phase of the study.

Analytical Methods: Buspirone and its active metabolite, 1-pyrimidinylpiperazine (1-PP), should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and quality control chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values. Successful completion of the studies described in this guidance is dependent on the use of an assay with a sufficient level of sensitivity to measure both buspirone and its active metabolite.

Statistical Analysis of Pharmacokinetic Data (Plasma): See Division of Bioequivalence guidance, Statistical *Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design or Replicated Treatment Designs.*

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports, and all incidents of possible adverse reactions to the study formulations should be reported.

D. Limited-Food-Effects Study

A limited-food-effects study should be performed in the same manner as the single-dose fasting study, with the following exceptions:

Procedures: Equal numbers of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design. Each subject will receive the following treatments:

Treatment 1: Generic product, buspirone HCl (2 x 15-mg tablets) administered after a standard breakfast.[4]

Treatment 2: Reference product (BuSpar), (2 x 15-mg tablets) administered after a standard breakfast.

Treatment 3: Generic product, (2 x 15-mg tablets) administered under fasting conditions.[5]

Following a ten-hour fast, subjects receiving treatments 1 and 2 should be served a standard breakfast. The subjects should have thirty minutes to finish the entire breakfast, then be immediately dosed with 2 x 15-mg tablets of the test or reference product with 240 mL of water. Subjects receiving Treatment 3 should be dosed with 2 x 15-mg tablets of the test product with 240 mL of water only. The same lots of the test and reference products used in the study under fasting conditions should be used in the food study. No other food should be allowed for at least four hours postdose. Water may be allowed after the first hour. Subjects should be served scheduled standardized meals throughout the study.

Statistical Analysis: In general, a comparable food effect will be assumed provided the AUC_{0-T}, $AUC_{0-\infty}$, and C_{max} mean values for the test product differ no more than 20 percent from the respective mean values obtained for the reference product in this study.

Retention of Samples: The laboratory conducting the bioequivalence tests should retain an appropriately identified reserve sample of the test product and the reference standard used to perform the in vivo bioequivalence study for approval of the application. Each reserve sample should consist of at least 200 dosage units. For more information please refer to 21 CFR 320.32.

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[4] Thirty minutes before drug administration, each subject should consume a standardized, high fat content meal consisting of:

One buttered English Muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

[5] For additional guidance in performing the food effect study for buspirone, please refer to the guidance for industry, *Food-Effect Bioavailability and Bioequivlence* (draft, 10/1997), once it has been finalized.

III. IN VITRO TESTING

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested in vivo. Because no official USP dissolution method is currently available for buspirone hydrochloride tablets, the FDA dissolution method should be followed. The following method and tolerances are currently recommended for this product:

Apparatus:	USP XXIII apparatus II (Paddle)
RPM:	50 RPM
Medium:	0.01N HCl at 37°C
Volume:	500 mL
Sampling Times:	10, 20, 30 and 45 minutes
Tolerance (Q):	NLT 80 percent in 30 minutes
Analytical:	As per USP XXIII, if available, or other validated method

The percent of the test and reference product dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXIII.

IV. WAIVERS

Waiver of in vivo bioequivalence study requirements for the 5-mg and 10-mg tablets of the generic product may be granted per 21 CFR 320.22(d)(2) provided *both* of the following conditions are met:

A. The 5-mg and 10-mg tablets are proportionally similar in both active and inactive ingredients to the 15-mg tablet that has demonstrated bioequivalence to the listed reference (15 mg) product in vivo.

B. The 5-mg and 10-mg strengths of the generic product meet the specified dissolution testing requirement.

REFERENCES

1. Goa, K.L. and A. Ward, "Buspirone: A Preliminary Review of its Pharmacological Properties and Therapeutic Efficacy as an Anxiolytic," *Drugs*, 32:114-29, 1986.

2. Taylor, D.P. "Buspirone: A New Approach to the Treatment of Anxiety," *FASEB*, 2:2445-52, 1988.

3. Murasaki, M., S. Miura, J. Ishigooka , et al., "Phase I Study of a New Antianxiety Drug, Buspirone," *Progress in Neuro-Psychopharmacol Biol Psychiat*,13:137-44, 1989.

4. Schuckit, M.A., "Clinical Studies of Buspirone," *Psychopathology*, 17 (suppl.3):61-8, 1984.

5. *Physician's Desk Reference.* 51st ed., Medical Economics Company, Oradell, N.J., 1997: pp. 738-40, 1997.

6. Riblet, L.A., A.S. Eison, M.S. Eison, et al., "Neuropharmacology of Buspirone," *Psychopathology*,17 (suppl.3):69-78, 1984.

7. Riblet, L.A., D.P. Taylor, M.S. Eison, et al., "Pharmacology and Neurochemistry of Buspirone," *J Clin Psychiatry*, 43:11-7, 1982.

8. Peroutka, S.J., "Selective Interaction of Novel Anxiolytics with 5-Hydroxytryptamine 1_A Receptors," *Biol Psychiatry*, 20:971-9, 1985.

9. Jann, M.W., "Buspirone: an Update on a Unique Anxiolytic Agent," *Pharmacotherapy*, 8:100-16, 1988.

10. Gammans, R.E., R.F. Mayol, and J.A. Labudde, "Metabolism and Disposition of Buspirone," *Am J Med*, 80:41-51, 1986.

11. Jajoo, H.K., R.F. Mayol, J.A. Labudde, and I.A. Blair, "Metabolism of the Antianxiety Drug Buspirone in Human Subjects," *Drug Metab Dispos*, 17:634-40, 1989.

12. Goldberg, H.L., "Buspirone Hydrochloride: A Unique New Anxiolytic Agent," *Pharmacotherapy*, 4:315-21, 1984.

13. Gammans, R.E., M.L. Westrick, J.P. Shea, et al., "Pharmacokinetics of Buspirone in Elderly Subjects," *J Clin Pharmacol*, 29:72-8, 1989.

14. Bullen, W.W., D.L. Bivens, R.E. Gammans, and J.A. LaBudde, "The Binding of Buspirone to Human Plasma Proteins," *Federation Proceeding*,44:1123, 1985.

15. Kastenholz ,K.V., and M.L. Crismon, "Buspirone, a Novel Nonbenzodiazepine Anxiolytic," *Clin Pharmacy*,3:600-607, 1984.

16. Gammans, R.E., R.F. Mayol, A.V. Mackenthun, and L.F. Sokya, "The Relationship Between Buspirone Bioavailability and Dose in Healthy Subjects," *Biopharmaceutics and Drug Dispososition*, 6:139-145.1, 1985.

17. Toothaker, R.D., and P.G. Welling, "The Effect of Food on Drug Bioavailability," *Annu Rev Pharmacol Toxicol*, 20:173-99, 1980.

18. Mayol, R.F., R.E. Gammans, A.V. Mackenthun, and L.F. Soyka, "The Effect of Food on the Bioavailability of Buspirone HCl," *Clin Research*, 31:631A, 1983.

APPENDIX 2

Study CN101-128: "Bioequivalence Between Unlabeled and Stable-Labeled Buspirone Hydrochloride Solutions when Administered Orally"

OBJECTIVES

To compare the rate and extent of absorption of the stable-labeled buspirone solution to that of the unlabeled buspirone solution (both administered simultaneously) to determine if an isotope effect exists on the pharmacokinetics of the stable-labeled drug.

FORMULATIONS

1) 30 mg Buspirone solution containing 15 mg (1 mg/mL) unlabeled buspirone plus 15 mg [13C, 15N2]buspirone (1 mg/mL). PIN# 9022-J030-141; Batch N99032

SUBJECTS

Six (6) healthy male subjects ranging in ages from 20-50 years enrolled and completed the study.

STUDY DESIGN

A single site, single-dose, open-label, one-period, two-treatment design. Following an overnight fast, each of the six healthy subjects received an oral solution containing 15 mg unlabeled buspirone and 15 mg [13C, 15N2]buspirone. The study subjects drank the solution through a straw, followed by 240 mL of water. Serial blood samples were taken over a 24-hour period and the plasma analyzed for buspirone, its active metabolite 1-pyrimidinylpiperazine (1-PP), and their corresponding stable-labeled analogs using a ——— assay. Blood samples for pharmacokinetic analysis were drawn at specified time points according to the following schedule:

*pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, and 24 hours after drug administration

ANALYTICAL METHODS

Plasma samples were assayed for buspirone, its active metabolite 1-PP, and their isotope analogs using a validated ——— method. Method validation and assay performance were found to be acceptable.

Specificity: The assay is specific for buspirone, 1-PP, and their stable isotope analogs with no significant interference peaks seen at the retention times of the analytes or of the internal standard in the chromatograms.

Sensitivity: The LLOQ for buspirone and [13C, 15N2]buspirone was — ng/mL, and — ng/mL for 1-PP and [13C, 15N2]1-PP.

Accuracy: Assay accuracy was within 5.5% of the nominal concentration values of — and — ng/mL for buspirone and [13C, 15N2]buspirone, and — ng/mL for 1-PP and [13C, 15N2]1-PP.

Precision: The intra-assay precision was within 8.4% RSD and inter-assay precision within 5.4% RSD for the concentration values of — and — ng/mL for buspirone and stable-isotope buspirone, and — for 1-PP and stable isotope 1-PP.

Linearity: Demonstrated with the calibration curves generated from — ng/mL to — ng/mL for buspirone and [13C, 15N2]buspirone, and from — ng/mL to — ng/mL for 1-PP and [13C, 15N2]1-PP.

Stability: Processed samples shown to be stable for at least 48 hours at RT.

DATA ANALYSIS

Pharmacokinetic parameters determined for buspirone and 1-PP (and stable isotope analogs) included Cmax, Tmax, AUC (inf), AUC (0-t), and T1/2. A point estimate and 90% confidence interval were constructed for the geometric mean ratio (unlabeled: stable labeled) of Cmax and AUC (inf). The PK parameters were log-transformed and the resulting point and interval estimates were exponentiated to express the results as geometric means and ratios of geometric means. Lack of an isotope effect between unlabeled and stable labeled buspirone was to be concluded if the 90% confidence intervals of the ratios of Cmax and AUC (inf) geometric means for buspirone and its active metabolite 1-PP were contained entirely in the range of 0.80-1.25.

RESULTS

Figure 1 shows the structure of the stable-labeled buspirone used in this study. Table 1.1 and Table 1.2 show the mean plasma concentration-time data for buspirone ([13C, 15N2]buspirone) and its active metabolite 1-PP ([13C, 15N2]1-PP), respectively. Graphs for concentration vs. time profiles of buspirone and 1-PP are shown in Figure 2. Finally, the statistical results of the study are shown in Table 2 with point estimates and 90% confidence intervals. Tables 3 and 4 show the individual mean PK parameters for buspirone and 1-PP, respectively, for all study subjects. The median Tmax was 0.5 hours and 0.63 hours for stable-labeled and unlabeled buspirone, respectively. The median Tmax was 0.75 hours for both stable-labeled and unlabeled 1-PP.

Figure 1 Structure of [^{13}C,$^{15}N_2$]buspirone.

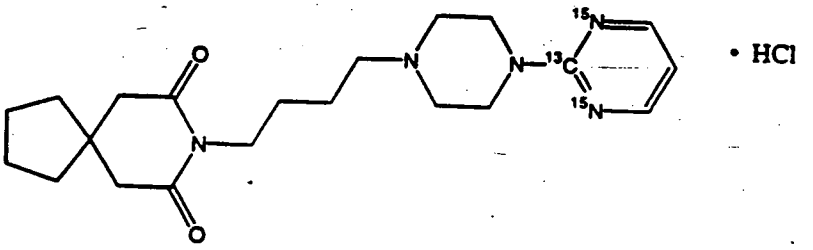


Table 1.1 Mean plasma concentration-time data for buspirone following administration of buspirone solution.

TIME			MEAN PLASMA CONCN (NG/ML)						
			Buspirone			[^{13}C,$^{15}N_2$]Buspirone			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	6	0.00	0.00	.	6	0.00	0.00	.
.	.	15	6	0.31	0.11	35.26	6	0.31	0.11	34.18
.	.	30	6	0.67	0.31	46.48	6	0.68	0.30	43.84
.	.	45	6	0.54	0.20	37.57	6	0.55	0.21	37.97
.	1	0	6	0.49	0.20	40.75	6	0.50	0.20	40.29
.	1	30	6	0.56	0.26	46.14	6	0.58	0.27	46.31
.	2	0	6	0.38	0.16	41.52	6	0.39	0.16	40.96
.	2	30	6	0.37	0.17	46.99	6	0.37	0.16	44.03
.	3	0	6	0.26	0.13	48.17	6	0.28	0.13	46.89
.	4	0	6	0.23	0.15	64.10	6	0.24	0.16	66.79
.	6	0	6	0.09	0.05	55.32	6	0.09	0.05	55.01
.	7	0	6	0.06	0.03	48.08	6	0.07	0.03	51.07
.	8	0	6	0.05	0.02	48.83	6	0.05	0.02	42.81
.	10	0	6	0.02	0.01	57.31	6	0.02	0.02	114.77
.	12	0	6	0.01	0.01	156.93	6	0.01	0.01	156.25
.	24	0	6	0.00	0.00	.	6	0.00	0.00	.

NOTE: VALUES <LLQ = 0

Source: Appendix 11.1.1B

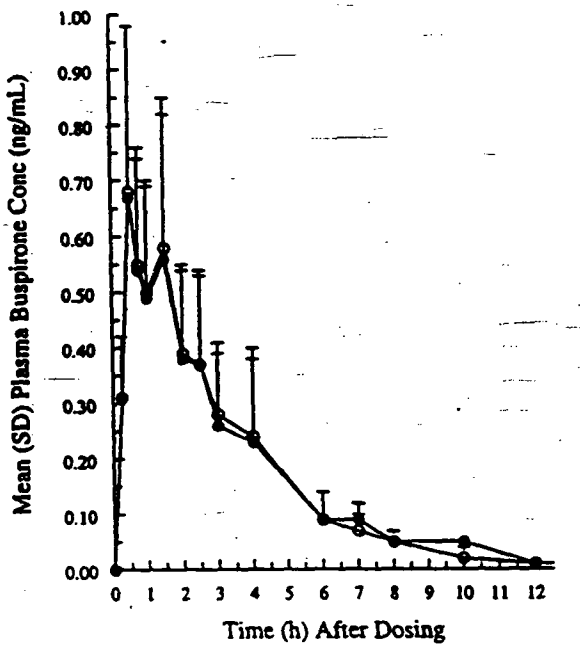
Table 1.2 Mean plasma concentration-time data for 1-PP following administration of buspirone solution.

TIME			MEAN PLASMA CONCN (NG/ML)						
			1-PP			[^{13}C,$^{15}N_2$]1-PP			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	6	0.00	0.00	.	6	0.00	0.00	.
.	.	15	6	1.57	1.61	102.59	6	1.69	1.61	95.29
.	.	30	6	5.17	2.50	48.24	6	5.45	2.44	44.76
.	.	45	6	5.83	1.96	33.65	6	6.13	1.97	32.13
.	1	0	6	5.76	1.57	27.26	6	6.12	1.57	25.66
.	1	30	6	5.50	1.05	19.15	6	5.86	1.04	17.72
.	2	0	6	5.54	1.00	18.04	6	5.90	1.13	19.15
.	2	30	6	5.12	0.92	17.92	6	5.49	0.95	17.34
.	3	0	6	4.85	0.78	16.19	6	5.31	0.93	17.48
.	4	0	6	4.87	0.91	18.74	6	5.12	0.98	19.20
.	6	0	6	3.86	1.24	32.12	6	4.05	1.19	29.42
.	7	0	6	3.56	1.51	42.41	6	3.71	1.45	39.04
.	8	0	6	2.96	1.15	38.86	6	3.31	1.38	41.63
.	10	0	6	2.15	0.96	44.55	6	2.33	1.02	43.67
.	12	0	6	1.52	0.79	51.66	6	1.69	0.88	52.09
.	24	0	6	0.33	0.31	94.28	6	0.40	0.30	75.25

NOTE: VALUES <LLQ = 0

Source: Appendix 11.1.2B

Figure 2 **Mean (SD) concentration-time profiles for buspirone and 1-PP with (-●-) representing unlabeled and (-○-) representing stable-labeled analogues (Protocol CN101-128) (Vertical bars represent one standard deviation)**



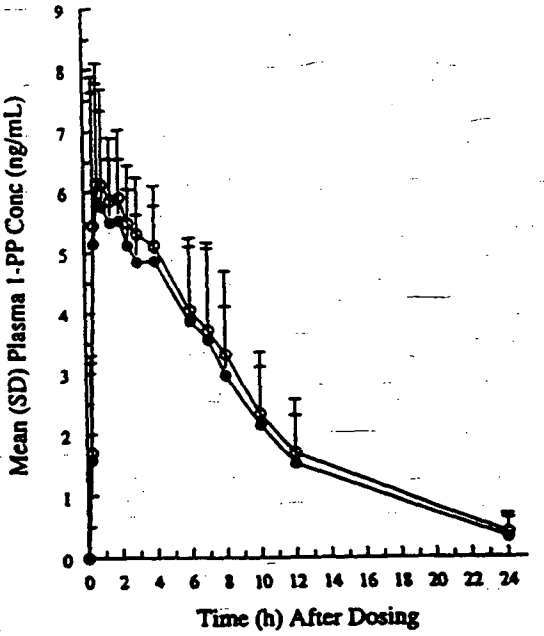


Table 2 **Relative bioavailability point estimates and 90% confidence intervals for C_{MAX} and AUC(INF) (Protocol CN101-128)**

Parameter[a]	Geometric Means		Ratios of Geometric Means	
	Buspirone	[^{13}C,$^{15}N_2$]Buspirone	Point Estimate	90% CI
Buspirone				
C_{MAX} (ng/mL)	0.66	0.66	0.99	(0.97, 1.01)
AUC(INF) (ng•h/mL)	1.96	2.01	0.97	(0.94, 1.01)
1-PP				
C_{MAX} (ng/mL)	7.02	7.25	0.97	(0.93, 1.01)
AUC(INF) (ng•h/mL)	53.31	58.10	0.92	(0.89, 0.95)

[a] C_{MAX} and AUC(INF) data were analyzed on a log scale; N=6

TABLE 3

Individual and arithmetic mean (SD) pharmacokinetic parameters for unlabeled and stable-labeled buspirone following the administration of buspirone solution.

PEAKNAME = BUSPIRONE

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
STUDY CENTER = 001						
0001	1					
0002	1					
0003	1					
0004	1					
0005	1					
0006	1					
MEAN		0.71	0.63*	2.06	2.14	2.76
SD		0.29	(0.50,1.50)	0.97	0.96	1.02
N		6	6	6	6	6

* MEDIAN (MINIMUM,MAXIMUM)

PEAKNAME = [^{13}C,$^{15}N_2$]BUSPIRONE

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
STUDY CENTER = 001						
0001	1					
0002	1					
0003	1					
0004	1					
0005	1					
0006	1					
MEAN		0.71	0.50*	2.06	2.20	3.04
SD		0.28	(0.50,1.50)	0.99	0.98	1.19
N		6	6	6	6	6

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 4

Individual and arithmetic mean (SD) pharmacokinetic parameters for unlabeled and stable-labeled 1-PP following the administration of buspirone solution.

PEAKNAME = 1-PP

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
PHARMACOKINETIC PARAMETER VALUES						
STUDY CENTER = 001						
0001	1					
0002	1					
0003	1					
0004	1					
0005	1					
0006	1					
MEAN		7.17	0.75*	52.76	56.18	4.92
SD		1.61	(0.50,7.00)	17.19	19.30	1.43
N		6	6	6	6	6

* MEDIAN (MINIMUM,MAXIMUM)

PEAKNAME = [^{13}C,$^{15}N_2$]1-PP

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
PHARMACOKINETIC PARAMETER VALUES						
STUDY CENTER = 001						
0001	1					
0002	1					
0003	1					
0004	1					
0005	1					
0006	1					
MEAN		7.40	0.75*	57.58	60.94	5.17
SD		1.62	(0.50,2.00)	17.48	20.33	1.14
N		6	6	6	6	6

* MEDIAN (MINIMUM,MAXIMUM)

CONCLUSIONS

There does not appear to be an isotope effect on the pharmacokinetics of buspirone when the isotope of the atoms in the molecule is changed to [13C, 15N2]. The pharmacokinetics of buspirone and its metabolite 1-PP are not significantly altered upon administration of the stable isotope moiety compared to the unlabeled moiety. This has been shown both through statistical analysis as well as the plasma concentration-time profiles.

APPEARS THIS WAY
ON ORIGINAL

Study CN101-126: "The Comparative Oral Bioavailability of 15 mg Buspirone Capsules and BuSpar Dividose 15 mg Tablets Using the Stable Label Technique in Healthy Subjects"

OBJECTIVES

To assess the bioequivalence of buspirone and its active metabolite 1-pyrimidinylpiperazine (1-PP) when buspirone is administered in equal doses as a capsule formulation and as the marketed BuSpar Dividose tablet formulation.

FORMULATIONS

Test Product:

1) Buspirone Capsules 15 mg (PIN# 9022-R015-135; Batch 9C13694), and
2) [13C, 15N2]Buspirone Solution 15 mg (PIN# 9022-J015-142; Batch N99040)

Reference Product:

1) Buspirone Tablets 15 mg (Batch A9J096A), and
2) [13C, 15N2]Buspirone Solution (PIN# 9022-J015-142; Batch N99040)

SUBJECTS

Forty-four healthy male (n=23) and female (n=21) subjects ranging in age from 18-50 years enrolled in the study. Of the forty-four subjects who were randomized to treatment in this study, forty-three completed both treatments.

STUDY DESIGN

A single site, single-dose, open-label, two-way crossover design. Subjects were randomized to one of two sequences of 22 subjects each. Following an overnight fast, each of the healthy subjects received 15 mg Buspirone capsule and 15 mg [13C, 15N2]buspirone solution simultaneously, or 15 mg BuSpar Dividose tablet and 15 mg [13C, 15N2]buspirone solution simultaneously, according to the randomization schedule. There was a 1-week washout between doses. Serial blood samples for pharmacokinetic analysis were collected prior to, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, and 24 hours after drug administration. The plasma was analyzed for buspirone, its active metabolite 1-pyrimidinylpiperazine (1-PP), and their corresponding stable-labeled analogs using a validated ——— assay.

ANALYTICAL METHODS

Plasma samples were assayed for buspirone, its active metabolite 1-PP, and their isotope analogs using a validated —— method. Method validation and assay performance were found to be acceptable.

Specificity: The assay is specific for buspirone, 1-PP, and their stable isotope analogs.

Sensitivity: The LLOQ for buspirone and [13C, 15N2]buspirone was — ng/mL, and — ng/mL for 1-PP and [13C, 15N2]1-PP.

Accuracy: Assay accuracy was within 6.2% of the nominal concentration values of —— ng/mL for buspirone and [13C, 15N2]buspirone, and — ng/mL for 1-PP and [13C, 15N2]1-PP.

Precision: The intra-assay precision was within 6.3% RSD and inter-assay precision within 4.7% RSD for the concentration values of —— , and —) ng/mL for buspirone and stable-isotope buspirone, and —— for 1-PP and stable isotope 1-PP.

DATA ANALYSIS

Pharmacokinetic parameters determined for buspirone and 1-PP (and stable isotope analogs) included Cmax, Tmax, AUC (inf), AUC (0-t), and T1/2. Relative Cmax and AUC (inf), defined as the ratios of unlabeled analyte to stable-labeled analyte, were also determined. A point estimate was calculated based on the ratio of Relative Cmax or AUC (inf) of the test (capsule) to reference (tablet). Subsequently, 90% confidence intervals were constructed for the ratio (test:reference) of relative Cmax and AUC (inf). Bioequivalence between the capsules and tablets was to be concluded if the 90% confidence intervals of the ratios of both relative Cmax and relative AUC (inf) geometric means for buspirone and its active metabolite 1-PP were contained entirely between 0.80-1.25.

RESULTS

Tables 1.1 and 1.2 show the mean plasma concentration-time data for buspirone and [13C, 15N2]buspirone, and 1-PP and [13C, 15N2]1-PP, respectively. Figure 1 shows the mean plasma concentration-time profiles for each treatment in the study. Tables 1.2 (A-D) show the statistical results from the data analysis of this study. Tables 2-9 show individual pharmacokinetic means for all study subjects for buspirone and 1-PP (stable-labeled and unlabeled). Finally, Figures 2-5 show subject profiles for relative Cmax and relative AUC (inf) versus formulation for each analyte.

Table 1.1 **Mean (SD) plasma concentration-time data for buspirone and [^{13}C,$^{15}N_2$]buspirone following administration of buspirone tablets and capsules concurrently with a [^{13}C,$^{15}N_2$]buspirone solution.**

			MEAN PLASMA CONCN OF BUSPIRONE (NG/ML)						
TIME			CAP + [^{13}C,$^{15}N_2$]buspirone Soln			TAB + [^{13}C,$^{15}N_2$]buspirone Soln			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	43	0.00	0.00	.	44	0.00	0.00	.
.	.	15	43	0.16	0.46	284.07	44	0.14	0.19	135.13
.	.	30	43	1.50	2.55	169.57	44	1.27	1.21	94.83
.	.	45	43	1.33	1.71	128.70	44	1.06	0.96	90.73
.	1	0	43	0.95	1.08	114.36	44	0.77	0.60	77.75
.	1	30	43	0.62	0.63	102.95	44	0.52	0.40	77.62
.	2	0	43	0.65	0.85	131.87	44	0.60	0.61	101.19
.	2	30	43	0.58	0.68	118.90	44	0.68	1.04	153.03
.	3	0	43	0.65	1.50	230.53	44	0.52	0.81	156.67
.	4	0	43	0.47	0.75	158.45	44	0.45	0.75	167.62
.	6	0	43	0.23	0.32	142.00	44	0.22	0.37	169.82
.	7	0	43	0.16	0.21	131.85	44	0.15	0.24	158.89
.	8	0	43	0.11	0.18	159.36	44	0.11	0.20	185.63
.	10	0	43	0.06	0.11	174.46	44	0.06	0.11	183.30
.	12	0	43	0.04	0.06	172.81	44	0.04	0.07	195.37
.	24	0	43	0.00	0.01	425.70	44	0.00	0.01	504.07

			MEAN PLASMA CONCN OF [^{13}C,$^{15}N_2$]BUSPIRONE (NG/ML)						
TIME			CAP + [^{13}C,$^{15}N_2$]buspirone Soln			TAB + [^{13}C,$^{15}N_2$]buspirone Soln			
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	43	0.00	0.00	.	44	0.00	0.00	.
.	.	15	43	0.94	1.12	118.85	44	0.73	0.61	83.22
.	.	30	43	2.32	3.13	135.08	44	2.08	2.10	100.84
.	.	45	43	1.80	1.82	100.94	44	1.65	1.32	79.70
.	1	0	43	1.35	1.21	89.46	44	1.22	0.76	62.12
.	1	30	43	0.85	0.61	72.23	44	0.80	0.51	64.20
.	2	0	43	0.74	0.48	64.76	44	0.76	0.57	74.30
.	2	30	43	0.61	0.43	69.99	44	0.70	0.76	108.49
.	3	0	43	0.51	0.41	79.99	44	0.53	0.55	102.87
.	4	0	43	0.42	0.42	98.71	44	0.42	0.46	108.66
.	6	0	43	0.22	0.22	97.94	44	0.21	0.26	120.34
.	7	0	43	0.15	0.13	86.88	44	0.15	0.16	106.81
.	8	0	43	0.11	0.12	107.96	44	0.11	0.13	126.68
.	10	0	43	0.07	0.08	115.62	44	0.06	0.07	124.42
.	12	0	43	0.04	0.04	120.42	44	0.04	0.06	148.81
.	24	0	43	0.00	0.01	425.39	44	0.00	0.01	512.97

NOTE: VALUES <LLQ = 0

Source: Appendix 11.1.1B

Table 1.2 **Mean (SD) plasma concentration-time data for 1-PP and [^{13}C,$^{15}N_2$]1-PP following administration of buspirone tablets and capsules concurrently with a [^{13}C,$^{15}N_2$]buspirone solution.**

			MEAN PLASMA CONCN OF 1-PP (NG/ML)					
TIME			CAP + [^{13}C,$^{15}N_2$]buspirone Soln			TAB + [^{13}C,$^{15}N_2$]buspirone Soln		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	43	0.00	0.00	.	44	0.00	0.02	663.32
.	.	15	43	0.20	0.38	189.87	44	0.45	0.79	175.34
.	.	30	43	4.15	3.82	92.19	44	4.34	3.27	75.27
.	.	45	43	5.34	2.90	54.22	44	5.50	3.20	58.10
.	1	0	43	5.34	2.52	47.11	44	5.29	2.73	51.63
.	1	30	43	5.27	2.36	44.88	44	5.05	2.59	51.26
.	2	0	43	5.22	2.30	44.00	44	5.17	2.29	44.31
.	2	30	43	5.12	2.32	45.27	44	5.26	2.41	45.88
.	3	0	43	5.06	2.32	45.78	44	5.13	2.54	49.46
.	4	0	43	4.73	2.38	50.19	44	4.54	2.34	51.59
.	6	0	43	3.72	2.35	63.34	44	3.76	2.30	61.24
.	7	0	43	3.36	2.30	68.34	44	3.37	2.41	71.55
.	8	0	43	3.07	2.31	75.02	44	3.00	2.33	77.62
.	10	0	43	2.35	2.10	89.45	44	2.32	2.02	87.04
.	12	0	43	1.91	1.93	100.75	44	1.89	1.84	97.44
.	24	0	43	0.61	0.89	146.14	44	0.56	0.78	138.94

			MEAN PLASMA CONCN OF [^{13}C,$^{15}N_2$]1-PP (NG/ML)					
TIME			CAP + [^{13}C,$^{15}N_2$]buspirone Soln			TAB + [^{13}C,$^{15}N_2$]buspirone Soln		
DAY	HR	MIN	N	MEAN	SD	%RSD	N	MEAN	SD	%RSD
.	.	0	43	0.00	0.03	655.74	44	0.00	0.00	.
.	.	15	43	1.29	1.56	120.31	44	1.21	1.42	116.82
.	.	30	43	6.26	3.50	55.88	44	5.80	3.35	57.71
.	.	45	43	6.91	2.78	40.17	44	6.65	2.79	41.92
.	1	0	43	6.59	2.42	36.73	44	6.24	2.39	38.22
.	1	30	43	6.13	2.27	37.09	44	5.90	2.40	40.65
.	2	0	43	5.81	2.35	40.45	44	5.77	2.32	40.22
.	2	30	43	5.54	2.39	43.06	44	5.66	2.45	43.23
.	3	0	43	5.33	2.45	45.97	44	5.39	2.60	48.33
.	4	0	43	4.89	2.55	52.14	44	4.74	2.49	52.47
.	6	0	43	3.87	2.58	66.61	44	3.89	2.55	65.57
.	7	0	43	3.51	2.50	71.28	44	3.50	2.56	73.09
.	8	0	43	3.16	2.45	77.54	44	3.13	2.55	81.44
.	10	0	43	2.39	2.14	89.71	44	2.38	2.14	89.77
.	12	0	43	1.95	2.00	102.87	44	1.93	1.94	100.62
.	24	0	43	0.62	0.94	151.66	44	0.57	0.83	146.13

NOTE: VALUES <LLQ = 0

Source: Appendix 11.1.2B

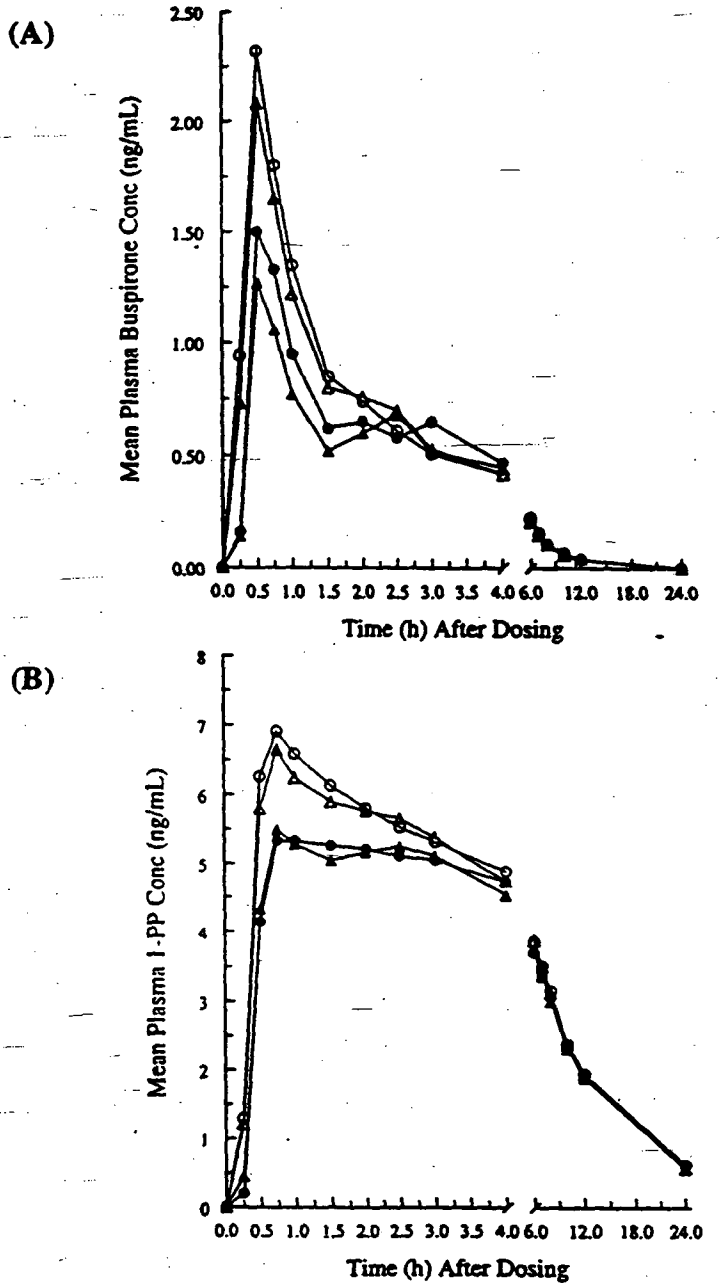


Figure 1 **The mean concentration-time profiles for (A) buspirone and stable-labeled buspirone, and (B) 1-PP and stable-labeled 1-PP (N=43) with (-●-) representing tablets (reference), (-○-) representing stable-labeled buspirone solution co-administered with the tablets, (-▲-) representing capsules (test), and (-Δ-) representing stable-labeled buspirone solution co-administered with the capsules**

Table 1.2A **Summary of statistical analysis results for buspirone Relative CMAX and AUC**

Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means	
	Capsule	Tablet	Pt. Estimate	90% C.I.
Relative CMAX	0.64	0.63	1.02	(0.92, 1.13)
Relative AUC(INF)	0.67	0.68	0.98	(0.92, 1.05)

Source: Tables 4A,5A of Appendix 6.4

Table 1.2B **Summary of other (unlabeled) buspirone pharmacokinetic parameters**

Buspirone Parameter	Buspirone Treatment Codes	
	Tablet	**Capsule**
TMAX (h) Median (range)	0.75	0.75
T-HALF (h) Mean (SD)	3.22 (1.95)	2.94 (1.32)

Source: Tables 3A of Appendix 6.4

Table 1.2C **Summary of statistical analysis results for 1-PP Relative CMAX and AUC.**

Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means	
	Capsule	Tablet	Pt. Estimate	90% C.I.
Relative CMAX	0.89	0.91	0.98	(0.93, 1.03)
Relative AUC(INF)	0.94	0.95	0.99	(0.98, 1.01)

Source: Tables 6A,7A of Appendix 6.4

Table 1.2D **Summary of other (unlabeled) 1-PP pharmacokinetic parameters**

Buspirone Parameter	Buspirone Treatment Codes	
	Tablet	**Capsule**
TMAX (h) Median (range)	1.00	1.00
T-HALF (h) Mean (SD)	5.60 (2.36)	5.78 (2.77)

Source: Tables 3B of Appendix 6.4

TABLE 2

Individual and arithmetic mean (SD) pharmacokinetic parameters for buspirone following the administration of 1x15 mg buspirone capsule concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = Buspirone; Treatment=1x15 mg Buspirone Capsule

		PHARMACOKINETIC PARAMETER VALUES						
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)	REL CMAX	REL AUC
0001	2							
0002	1							
0003	2							
0004	1							
0005	1							
0006	2							
0007	2							
0008	1							
0009	2							
0010	1							
0011	1							
0013	2							
0014	1							
0015	1							
0016	2							
0017	2							
0018	1							
0019	2							
0020	1							
0021	2							
0022	1							
0023	1							
0024	2							
0025	2							
0026	1							
0027	1							
0028	2							
0029	1							
0030	2							
0031	1							
0032	2							
0033	1							
0034	2							
0035	2							
0036	1							
0037	2							
0038	1							
0039	1							
0040	2							
0041	2							
0042	1							
0043	2							
0044	1							
MEAN		1.98	0.75*	4.10	4.28	2.94	0.690	0.714
SD		2.60	(0.50,4.00)	5.44	5.50	1.32	0.252	0.266
N		43	43	43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 3

Individual and arithmetic mean (SD) pharmacokinetic parameters for buspirone following the administration of 1x15 mg BuSpar® Dividose® tablet concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = Buspirone; Treatment=1x15 mg BuSpar® Dividose® Tablet

		PHARMACOKINETIC PARAMETER VALUES						
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)	REL CMAX	REL AUC
0001	2							
0002	1							
0003	2							
0004	1							
0005	1							
0006	2							
0007	2							
0008	1							
0009	2							
0010	1							
0011	1							
0013	2							
0014	1							
0015	1							
0016	2							
0017	2							
0018	1							
0019	2							
0020	1							
0021	2							
0022	1							
0023	1							
0024	2							
0025	2							
0026	1							
0027	1							
0028	2							
0029	-							
0030	2							
0031	1							
0032	2							
0033	1							
0034	2							
0035	2							
0036	1							
0037	2							
0038	1							
0039	1							
0040	2							
0041	2							
0042	1							
0043	2							
0044	1							
MEAN		1.58	0.75*	3.69	3.87	3.22	0.692	0.708
SD		1.29	(0.50,6.00)	4.58	4.68	1.95	0.308	0.237
N		43	43	43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 4

Individual and arithmetic mean (SD) pharmacokinetic parameters for [^{13}C,$^{15}N_2$]buspirone following the administration of 1x15 mg buspirone capsule concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = [^{13}C,$^{15}N_2$]Buspirone; Treatment=1x15 mg Capsule

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
			PHARMACOKINETIC PARAMETER VALUES			
0001	2					
0002	1					
0003	2					
0004	1					
0005	1					
0006	2					
0007	2					
0008	1					
0009	2					
0010	1					
0011	1					
0013	2					
0014	1					
0015	1					
0016	2					
0017	2					
0018	1					
0019	2					
0020	1					
0021	2					
0022	1					
0023	1					
0024	2					
0025	2					
0026	1					
0027	1					
0028	2					
0029	1					
0030	2					
0031	1					
0032	2					
0033	1					
0034	2					
0035	2					
0036	1					
0037	2					
0038	1					
0039	1					
0040	2					
0041	2					
0042	1					
0043	2					
0044	1					
MEAN		2.51	0.50*	4.73	4.94	3.28
SD		3.08	(0.25,1.50)	4.31	4.38	2.23
N		43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 5

Individual and arithmetic mean (SD) pharmacokinetic parameters for [^{13}C,$^{15}N_2$]buspirone following the administration of 1x15 mg BuSpar® Dividose® tablet concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = [^{13}C,$^{15}N_2$]Buspirone; Treatment=1x15 mg BuSpar® Dividose® Tablet

		PHARMACOKINETIC PARAMETER VALUES				
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	2					
0002	1					
0003	2					
0004	1					
0005	1					
0006	2					
0007	2					
0008	1					
0009	2					
0010	1					
0011	1					
0013	2					
0014	1					
0015	1					
0016	2					
0017	2					
0018	1					
0019	2					
0020	1					
0021	2					
0022	1					
0023	1					
0024	2					
0025	2					
0026	1					
0027	1					
0028	2					
0029	1					
0030	2					
0031	1					
0032	2					
0033	1					
0034	2					
0035	2					
0036	1					
0037	2					
0038	1					
0039	1					
0040	2					
0041	2					
0042	1					
0043	2					
0044	1					
MEAN		2.24	0.50*	4.58	4.76	2.96
SD		2.06	(0.25,2.50)	4.13	4.22	1.20
N		43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 6

Individual and arithmetic mean (SD) pharmacokinetic parameters for 1-PP following the administration of 1x15 mg buspirone capsule concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = 1-PP; Treatment=1x15 mg Buspirone Capsule

		PHARMACOKINETIC PARAMETER VALUES						
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)	REL CMAX	REL AUC
0001	2							
0002	1							
0003	2							
0004	1							
0005	1							
0006	2							
0007	2							
0008	1							
0009	2							
0010	1							
0011	1							
0013	2							
0014	1							
0015	1							
0016	2							
0017	2							
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0035	2							
0036	1							
0037	2							
0038	1							
0039	1							
0040	2							
0041	2							
0042	1							
0043	2							
0044	1							
MEAN		7.08	1.00*	56.27	64.57	5.78	0.898	0.946
SD		2.71	(0.50,10.00)	40.48	53.29	2.77	0.131	0.047
N		43	43	43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 7

Individual and arithmetic mean (SD) pharmacokinetic parameters for 1-PP following the administration of 1x15 mg BuSpar® Dividose® tablet concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = 1-PP; Treatment=1x15 mg BuSpar® Dividose® Tablet

		PHARMACOKINETIC PARAMETER VALUES						
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)	REL CMAX	REL AUC
0001	2							
0002	1							
0003	2							
0004	1							
0005	1							
0006	2							
0007	2							
0008	1							
0009	2							
0010	1							
0011	1							
0013	2							
0014	1							
0015	1							
0016	2							
0017	2							
0018	1							
0019	2							
0020	1							
0021	2							
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0032	2							
0033	1							
0034	2							
0035	2							
0036	1							
0037	2							
0038	1							
0039	1							
0040	2							
0041	2							
0042	1							
0043	2							
0044	1							
MEAN		7.15	1.00*	56.25	63.57	5.60	0.918	0.952
SD		2.85	(0.50,7.00)	39.47	49.74	2.36	0.130	0.064
N		43	43	43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 9

Individual and arithmetic mean (SD) pharmacokinetic parameters for [^{13}C,$^{15}N_2$]1-PP following the administration of 1x15 mg BuSpar® Dividose® tablet concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = [^{13}C,$^{15}N_2$]1-PP; Treatment=1x15 mg BuSpar® Dividose® Tablet

		PHARMACOKINETIC PARAMETER VALUES				
SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	2					
0002	1					
0003	2					
0004	1					
0005	1					
0006	2					
0007	2					
0008	1					
0009	2					
0010	1					
0011	1					
0013	2					
0014	1					
0015	1					
0016	2					
0017	2					
0018	1					
0019	2					
0020	1					
0021	2					
0022	1					
0023	1					
0024	2					
0025	2					
0026	1					
0027	1					
0028	2					
0029	1					
0030	2					
0031	1					
0032	2					
0033	1					
0034	2					
0035	2					
0036	1					
0037	2					
0038	1					
0039	1					
0040	2					
0041	2					
0042	1					
0043	2					
0044	1					
MEAN		7.79	0.75*	59.68	67.30	5.36
SD		2.89	(0.50,3.00)	42.53	53.38	2.54
N		43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

TABLE-8

Individual and arithmetic mean (SD) pharmacokinetic parameters for [^{13}C,$^{15}N_2$]1-PP following the administration of 1x15 mg buspirone capsule concurrently with a 15mg [^{13}C,$^{15}N_2$]buspirone solution.

Analyte = [^{13}C,$^{15}N_2$]1-PP; Treatment=1x15 mg Capsule

SUBJ	SEQ	PHARMACOKINETIC PARAMETER VALUES				
		CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	2					
0002	1					
0003	2					
0004	1					
0005	1					
0006	2					
0007	2					
0008	1					
0009	2					
0010	1					
0011	1					
0013	2					
0014	1					
0015	1					
0016	2					
0017	2					
0018	1					
0019	2					
0020	1					
0021	2					
0022	1					
0023	1					
0024	2					
0025	2					
0026	1					
0027	1					
0028	2					
0029	1					
0030	2					
0031	1					
0032	2					
0033	1					
0034	2					
0035	2					
0036	1					
0037	2					
0038	1					
0039	1					
0040	2					
0041	2					
0042	1					
0043	2					
0044	1					
MEAN		7.90	0.75*	60.12	68.78	5.53
SD		2.71	(0.50,2.50)	43.54	57.19	2.78
N		43	43	43	43	43

* MEDIAN (MINIMUM,MAXIMUM)

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CONCLUSIONS

The capsule and tablet formulations of buspirone are shown to be bioequivalent based on the statistical analysis of the ratios of relative Cmax and relative AUC (inf) between the two formulations. The 90% confidence intervals for the ratios of relative Cmax and relative AUC (inf) geometric means were within the range of 0.80-1.25.

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Study CN101-127: "Food Effect Study of Buspirone Tablets, Capsules and Capsule Contents in Healthy Subjects"

OBJECTIVES

The objectives of the study were to:

1) Compare the effect of food between the capsule formulation and the marketed BuSpar Dividose tablets
2) Evaluate the effect of food when the capsule contents are sprinkled and mixed with applesauce for administration compared to the intact capsule formulation in the fed state
3) Determine the effect of food on the intact capsule formulation compared to the capsule in the fasted state.

FORMULATIONS

Test Product: Buspirone Capsules 15 mg (PIN# 9022-R015-135; Batch 9C13694)
Reference Product: Buspirone Tablets 15 mg (Batch A9J096A)

SUBJECTS

Forty-four healthy male (n=23) and female (n=21) subjects ranging in age from 18-50 years enrolled in the study. Of the forty-four subjects who were randomized to treatment in this study, forty completed both treatments.

STUDY DESIGN

A single site, single-dose, open-label, four-way crossover design. Subjects were randomized to one of four sequences of 11 subjects each. Following an overnight fast, each of the healthy subjects received buspirone either as 2 x 15 mg capsules or 2 x 15 mg tablets according to a randomization schedule of the following treatments:

TFED = 2 x 15 mg buspirone tablets 5 minutes after high-fat breakfast
CFED = 2 x 15 mg buspirone capsules 5 minutes after high-fat breakfast
CFAS = 2 x 15 mg buspirone capsules under fasting conditions
OPEN = 2 x 15 mg buspirone capsules 5 minutes after high-fat breakfast with the capsules opened and contents sprinkled and mixed in 1 ounce of applesauce

There was a 1-week washout between doses. Serial blood samples for pharmacokinetic analysis were collected prior to, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 10, 12, and 24 hours after drug administration. The plasma was analyzed for buspirone

and its active metabolite, 1-pyrimidinylpiperazine (1-PP), using a validated — assay.

ANALYTICAL METHODS

Plasma samples were assayed for buspirone and its active metabolite 1-PP using a validated — method. Method validation and assay performance was found to be acceptable.

Sensitivity: The LLOQ for buspirone was — ng/mL and — ng/mL for 1-PP.

Accuracy: Assay accuracy for buspirone was within 3.7% of the nominal concentration values of — ng/mL, and within 7.9% of the nominal concentration values of — ng/mL for 1-PP.

Precision: The intra-assay precision was within 3.6% RSD and inter-assay precision within 3.7% RSD for the concentration values of — and — ng/mL for buspirone, and — for 1-PP.

DATA ANALYSIS

Pharmacokinetic parameters determined for buspirone and 1-PP included Cmax, Tmax, AUC (inf), AUC (0-t), and T1/2. To compare the effect of food on the bioavailability of buspirone treatments, an analysis of variance (ANOVA) appropriate for a four-way crossover study was performed on log-transformed values of AUC (inf), AUC (0-t), and Cmax for buspirone and 1-PP. The sponsor refers to the FDA Guidance entitled: "Buspirone Hydrochloride Tablets In Vivo Bioequivalence and In Vitro Dissolution Testing". The Guidance states: "In general, a comparable food effect will be assumed provided the AUC (0-t), AUC (inf), and Cmax mean values for the test product differ no more than 20% from the respective mean values obtained for the reference product in the study." Comparability of food effect between capsules and tablets (treatments CFED vs. TFED) was to be concluded by the sponsor if the geometric means for Cmax, AUC (0-t), and AUC (inf) of buspirone and 1-PP were within 20% of each other. Similarly, comparability of food effect between opened capsule contents and intact capsules (treatments OPEN vs. CFED) was to be concluded by the sponsor if the geometric means for Cmax, AUC (0-t), and AUC (inf) of buspirone and 1-PP were within 20% of each other.

The sponsor also examined the geometric mean comparisons for Cmax, AUC (0-t), and AUC (inf) of intact capsules in the fed and fasted states (treatments CFED vs. CFAS) as well as the capsule contents in the fed state to the intact capsules in the fasted state (treatment OPEN vs. CFAS). Finally, the sponsor compared the geometric mean values for Cmax, AUC (0-t), and AUC (inf) for the capsule contents and the tablets

under the fed state (treatments OPEN vs. TFED). In addition to the +/- 20% criteria to demonstrate comparable food effects between treatments, the sponsor determined the point estimates and 90% confidence intervals for the ratios of geometric mean data.

RESULTS

The pharmacokinetic results of the study and treatment comparisons are shown in Tables 1-3 and Figure 1. The individual mean pharmacokinetic parameters for each treatment are shown in Tables 4-11:

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TABLE 1

Buspirone			
Treatment	*Pharmacokinetic Variable*		
	CMAX (ng/mL) Geometric Mean	AUC(INF) (ng·h/mL) Geometric Mean	AUC(0-T) (ng·h/mL) Geometric Mean
TFED	4.12	10.93	10.07
CFAS	2.13	4.55	3.68
CFED	2.88	9.83	9.00
OPEN	4.27	12.69	11.71
Treatment Comparison	**%Difference of Test Geometric Mean from Reference Geometric Mean**		
	CMAX	AUC(INF)	AUC(0-T)
CFED vs TFED[a]	-30%	-10%	-11%
OPEN vs CFED[a]	48%	29%	30%
OPEN vs CFAS[b]	101%	179%	218%
CFED vs CFAS[b]	35%	116%	145%
OPEN vs TFED[c]	4%	16%	16%
1-PP			
Treatment	*Pharmacokinetic Variable*		
	CMAX (ng/mL) Geometric Mean	AUC(INF) (ng·h/mL) Geometric Mean	AUC(0-T) (ng·h/mL) Geometric Mean
TFED	10.84	79.62	74.27
CFAS	13.46	80.11	74.73
CFED	9.12	76.76	71.71
OPEN	9.28	80.23	74.66
Treatment Comparison	**% Difference of Test Geometric Mean from Reference Geometric Mean**		
	CMAX	AUC(INF)	AUC(0-T)
CFED vs TFED[a]	-16%	-4%	-4%
OPEN vs CFED[a]	2%	5%	4%
OPEN vs CFAS[b]	-31%	0%	0%
CFED vs CFAS[b]	-32%	-4%	-4%
OPEN vs TFED[c]	-14%	1%	1%

[a]Primary comparison; [b]Secondary comparison; [c]*Post hoc* comparison

Results for TMAX and T-HALF for buspirone and 1-PP are provided below:

Analyte	Parameter	Treatment			
		CFAS	CFED	OPEN	TFED
Buspirone	TMAX (h) Median (range)	0.75	1.50	0.75	1.00
	T-HALF (h) Mean (SD)	3.01 (1.84)	3.26 (1.90)	3.66 (1.85)	3.92 (3.04)
1-PP	TMAX (h) Median (range)	0.75	3.00	2.50	2.00
	T-HALF (h) Mean (SD)	4.78 (1.85)	4.55 (1.37)	4.77 (1.37)	4.62 (1.70)

TABLE 2

Summary of Statistical Analysis Results for Buspirone CMAX and AUC

	Pharmacokinetic Variable		
Treatment	CMAX (ng/mL) Geometric Mean	AUC(INF) ng·h/mL) Geometric Mean	AUC(0-T) (ng·h/mL) Geometric Mean
TFED	4.12	10.93	10.07
CFAS	2.13	4.55	3.68
CFED	2.88	9.83	9.00
OPEN	4.27	12.69	11.71
Treatment Comparison	**Point Estimate and 90% C.I. for Ratio of Geometric Means for CMAX (ng/mL)**	**AUC(INF) (ng·h/mL)**	**AUC(0-T) (ng·h/mL)**
CFED vs TFED	0.70 (0.57, 0.86)	0.90 (0.76, 1.06)	0.89 (0.74, 1.08)
OPEN vs CFED	1.48 (1.21, 1.82)	1.29 (1.10, 1.52)	1.30 (1.08, 1.57)
OPEN vs TFED	1.04 (0.84, 1.27)	1.16 (0.99, 1.37)	1.16 (0.97, 1.40)
OPEN vs CFAS	2.01 (1.63, 2.47)	2.79 (2.37, 3.28)	3.18 (2.65, 3.83)
CFED vs CFAS	1.35 (1.10, 1.67)	2.16 (1.84, 2.54)	2.45 (2.03, 2.95)

Source: Tables 4,5,6.

TABLE 3

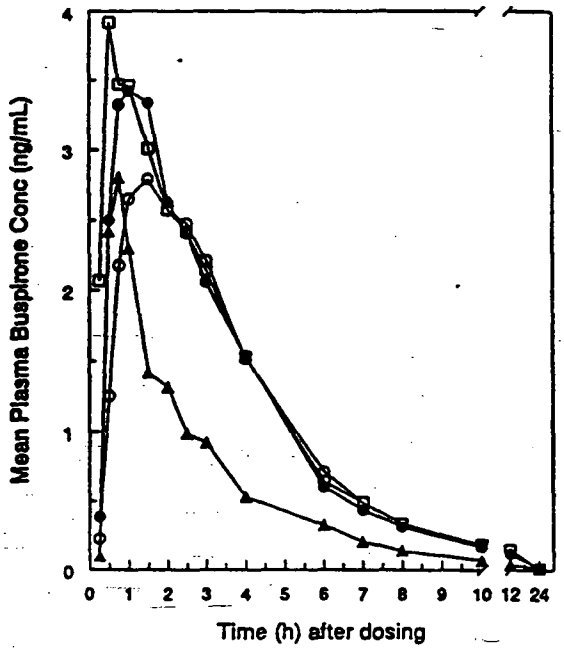
Summary of Statistical Analysis Results for 1-PP CMAX and AUC

	Pharmacokinetic Variable		
Treatment	CMAX (ng/mL) Geometric Mean	AUC(INF) ng·h/mL) Geometric Mean	AUC(0-T) (ng·h/mL) Geometric Mean
TFED	10.84	79.62	74.27
CFAS	13.46	80.11	74.73
CFED	9.12	76.76	71.71
OPEN	9.28	80.23	74.66
Treatment Comparison	**Point Estimate and 90% C.I. for Ratio of Geometric Means for CMAX (ng/mL)**	**AUC(INF) (ng·h/mL)**	**AUC(0-T) (ng·h/mL)**
CFED vs TFED	0.84 (0.78, 0.91)	0.96 (0.91, 1.02)	0.96 (0.92, 1.02)
OPEN vs CFED	1.02 (0.95, 1.10)	1.05 (0.99, 1.10)	1.04 (0.99, 1.10)
OPEN vs TFED	0.86 (0.80, 0.92)	1.01 (0.96, 1.06)	1.01 (0.95, 1.06)
OPEN vs CFAS	0.69 (0.64, 0.74)	1.00 (0.95, 1.06)	1.00 (0.95, 1.05)
CFED vs CFAS	0.68 (0.63, 0.73)	0.96 (0.91, 1.01)	0.96 (0.91, 1.01)

Source: Tables 7,8,9.

Figure 1

The mean concentration-time profiles for buspirone and 1-PP were as follows with (-●-) representing TFED, (-▲-) representing CFAS, (-○-) representing CFED, and (-□-) representing OPEN:



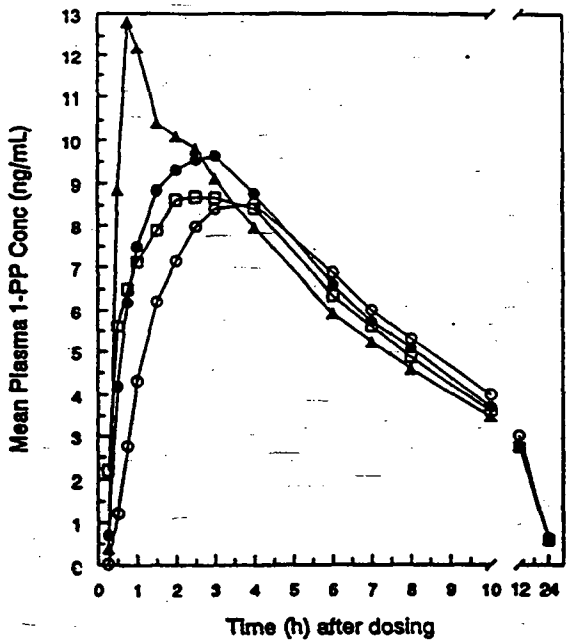


TABLE 4

Individual and arithmetic mean (SD) pharmacokinetic parameter values for buspirone following the administration of 2x15 mg BuSpar® Dividose® tablets 5 min after a high-fat breakfast

Analyte = Buspirone; Treatment = TFED

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		5.22	1.00*	12.67	13.65	3.92
SD		3.84	(0.50,4.00)	10.21	10.59	3.04
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 5

Individual and arithmetic mean (SD) pharmacokinetic parameter values for buspirone following the administration of 2x15 mg buspirone capsules after an overnight fast

Analyte = Buspirone; Treatment = CF[illegible]

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		3.57	0.75*	6.84	7.41	3.01
SD		3.86	(0.50,2.00)	8.60	8.81	1.84
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 6

Individnal and arithmetic mean (SD) pharmacokinetic parameter values for buspirone following the administration of 2x15 mg buspirone capsules 5 min after a high-fat breakfast

Analyte = Buspirone; Treatment = CFED

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		4.17	1.50*	12.82	13.67	3.26
SD		3.95	(0.25,4.00)	13.68	14.12	1.90
N		40	40	40	40	40

PHARMACOKINETIC PARAMETER VALUES

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 7

Individual and arithmetic mean (SD) pharmacokinetic parameter values for buspirone following administration of 2x15 mg buspirone capsules contents mixed into 1 oz of applesauce and eaten 5 min after a high-fat breakfast

Analyte = Buspirone; Treatment = OPEN

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	-					
0041	-					
0042	-					
0043	3					
0044	4					
MEAN		4.98	0.75*	14.45	15.35	3.66
SD		3.20	(0.25,3.00)	10.61	10.90	1.85
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 8

Individual and arithmetic mean (SD) pharmacokinetic parameter values for 1-PP following the administration of 2x15 mg BuSpar® Dividose® tablets 5 min after a high-fat breakfast

Analyte = 1-PP; Treatment = TFED

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		11.59	2.00*	87.26	94.73	4.62
SD		4.04	(0.50,6.00)	50.61	59.59	1.70
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 9

Individual and arithmetic mean (SD) pharmacokinetic parameter values for 1-PP following the administration of 2x15 mg buspirone capsules after an overnight fast

Analyte = 1-PP; Treatment = CFAS

SUBJ	SEQ	CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
		PHARMACOKINETIC PARAMETER VALUES				
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		14.58	0.75*	90.28	98.63	4.78
SD		5.44	(0.50,4.00)	57.77	72.87	1.85
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 10

Individual and arithmetic mean (SD) pharmacokinetic parameter values for 1-PP following the administration of 2x15 mg buspirone capsules 5 min after a high-fat breakfast

Analyte = 1-PP; Treatment = CFED

SUBJ	SEQ	PHARMACOKINETIC PARAMETER VALUES				
		CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	3					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		9.78	3.00*	84.79	91.31	4.55
SD		3.41	(0.50,6.00)	48.15	55.50	1.37
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

TABLE 11

Individual and arithmetic mean (SD) pharmacokinetic parameter values for 1-PP following administration of 2x15 mg buspirone capsules contents mixed into 1 oz of applesauce and eaten 5 min after a high-fat breakfast

Analyte = 1-PP; Treatment = OPEN

SUBJ	SEQ	PHARMACOKINETIC PARAMETER VALUES				
		CMAX (NG/ML)	TMAX (H)	AUC(0-T) (NG.H/ML)	AUC(INF) (NG.H/ML)	T-HALF (H)
0001	3					
0002	4					
0003	1					
0004	2					
0005	2					
0007	3					
0008	1					
0009	3					
0010	1					
0011	4					
0013	4					
0014	2					
0015	2					
0016	1					
0017	4					
0018	2					
0020	3					
0021	2					
0022	1					
0023	3					
0024	4					
0025	2					
0027	4					
0028	1					
0029	2					
0030	3					
0031	4					
0032	1					
0033	4					
0034	2					
0035	1					
0036	3					
0037	3					
0038	1					
0039	4					
0040	2					
0041	1					
0042	2					
0043	3					
0044	4					
MEAN		9.64	2.50*	85.71	92.58	4.77
SD		3.00	(0.50,7.00)	47.03	54.24	1.37
N		40	40	40	40	40

* MEDIAN (MINIMUM,MAXIMUM)

CONCLUSIONS

There is a food effect seen when the capsules are taken with food compared to fasting conditions (i.e. CFED and CFAS treatments). The table shows that taking the capsules in the fed state results in a 17% increase in Cmax, and an 84% increase in AUC (inf). The sponsor has determined the 90% confidence intervals for the different treatment comparisons. For CFED vs. CFAS, the values for Cmax and AUC (inf) were (1.10, 1.67), and (1.84, 2.54), respectively. The values are considerably outside the 0.80-1.25 confidence range typically used to demonstrate comparable food-effects. For the metabolite 1-PP, the Cmax decreased 33% when the capsules were administered under fed conditions compared to fasting conditions. The AUC values for 1-PP were basically unchanged between the CFED and CFAS treatments.

The capsules under fed conditions compared to the tablets under fed conditions (i.e. CFED vs. TFED) showed a mean decrease in buspirone levels of 20% in Cmax while AUC (inf) were comparable. There was no significant effect on 1-PP levels (< 20%) between the CFED and TFED treatments.

Opening the capsules and mixing the contents with applesauce showed minor differences in pharmacokinetic parameters when compared to the intact capsules under the fed state (i.e. OPEN vs. CFED). Pharmacokinetic parameters Cmax and AUC (inf) increased 19% and 12%, respectively, between the OPEN and CFED treatments. There was no significant effect on 1-PP levels between the OPEN and CFED treatments.

There were increases in Cmax and AUC (inf) when comparing the capsule contents mixed with food to the capsules under fasting conditions (i.e. OPEN vs. CFAS). Increases of 40% and 2-fold were seen with parameters Cmax and AUC (inf), respectively. The Cmax for 1-PP decreased 34% between the OPEN and CFAS treatment arms, but AUC values did not differ significantly.

Finally, the sponsor showed that pharmacokinetic parameters for the capsule contents mixed with applesauce under fed conditions closely resembled the parameters seen for the referenced tablets under fed conditions (i.e. OPEN vs. TFED). All PK parameters were within +/- 20% between the two treatments.

The Tmax and half-life for buspirone and its active metabolite 1-PP are shown in Table 1 under the Results section. The parameters Tmax and half-life appear to be similar between all treatments for buspirone and 1-PP, except for the Tmax of 1-PP between the CFED and CFAS treatment arms. The median Tmax under CFAS for 1-PP was 0.75 hours while under CFED was 3.00 hours. The ranges were similar, however this difference may not be clinically significant for a chronically administered medication.

APPENDIX 3

II Drug Product

FORMULATION DEVELOPMENT HISTORY (cont.)

Table II.T01 Composition for BuSpar® (buspirone hydrochloride, USP) Capsules

Potency	5 mg	7.5 mg	10 mg	15 mg
Ingredient	Amount in mg/Capsule			
Buspirone HCl	5.00	7.50	10.00	15.00
Microcrystalline Cellulose, NF	—			
Lactose, Anhydrose, NF	—			
Colloidal Silicon Dioxide, NF	—			
Sodium Starch Glycolate, NF	—			
Magnesium Stearate, NF	—			
Total Fill Weight (mg)	100.00	150.00	200.00	300.00
# 4 Capsule	√			
# 3 Capsule		√		
# 2 Capsule			√	
# 1 Capsule				√

II. Drug Product

J. Dissolution Comparison

In support of a waiver for bioequivalence testing for BuSpar® (buspirone hydrochloride, USP) 5 mg, 7.5 mg, and 10 mg capsules, an *in vitro* dissolution testing was conducted on these strengths. An *in vitro* dissolution testing was also conducted on the 15 mg capsule batch used for the bioequivalence studies.

A twelve-capsule dissolution profile for one batch (test batches) of BuSpar® 5 mg, 10 mg, and 15 mg capsules manufactured at Bristol-Myers Squibb Laboratories Company in Mayagüez, Puerto Rico was compared with the dissolution profile for a corresponding batch of tablets manufactured at the same facility (reference batches). A twelve-capsule dissolution profile for one batch of BuSpar® 7.5 mg capsules was also conducted but not compared as this strength is not available in tablet form.

Both the reference and test batches were tested for dissolution profiles in 0.01 N hydrochloric acid using USP apparatus 2 (paddles) at 50 rpm capable of maintaining a temperature of 37 ± 5°C. Aliquots were removed at 10, 20, 30, and 45-minute intervals and filtered prior to quantitation, which was achieved via liquid chromatography with a with an UV detector at 235 nm. The analytical methods used were 0311 and 248425, which is the current USP methodology for BuSpar® Tablets, with the appropriate modifications in the sampling time points. Methods are provided in section II.F.4.

The dissolution profiles were compared using the following equation that defines the similarity factor (f_2), as provided in SUPAC and Dissolution Testing of Immediate Release Solid Oral Dosage Forms guidance documents:

II. Drug Product

J. Dissolution Comparison

Individual dissolution results are shown in Tables II.J.T02 – II.J.T05. Results are also provided in graphical form in schematics II.J.S01 – II.J.S04.

Table II.J.T01 Dissolution Profile Comparison Between Capsule and Tablet Formulations Manufactured at Mayagüez, PR Facility

Reference Batches (tablets)			Test Batches (capsules)			
Lot Number	Strength	Batch Size (tablets)	Lot Number	Strength	Batch Size (capsules)	f_2 (50-100)
9D16972	5 mg	—	9C18038	5 mg	—	56
9F14340	10 mg	—	9C14476	10 mg	—	54
A9J096A	15 mg	—	9C13694	15 mg	—	54

II. Drug Product

J. Dissolution Comparison (cont.)

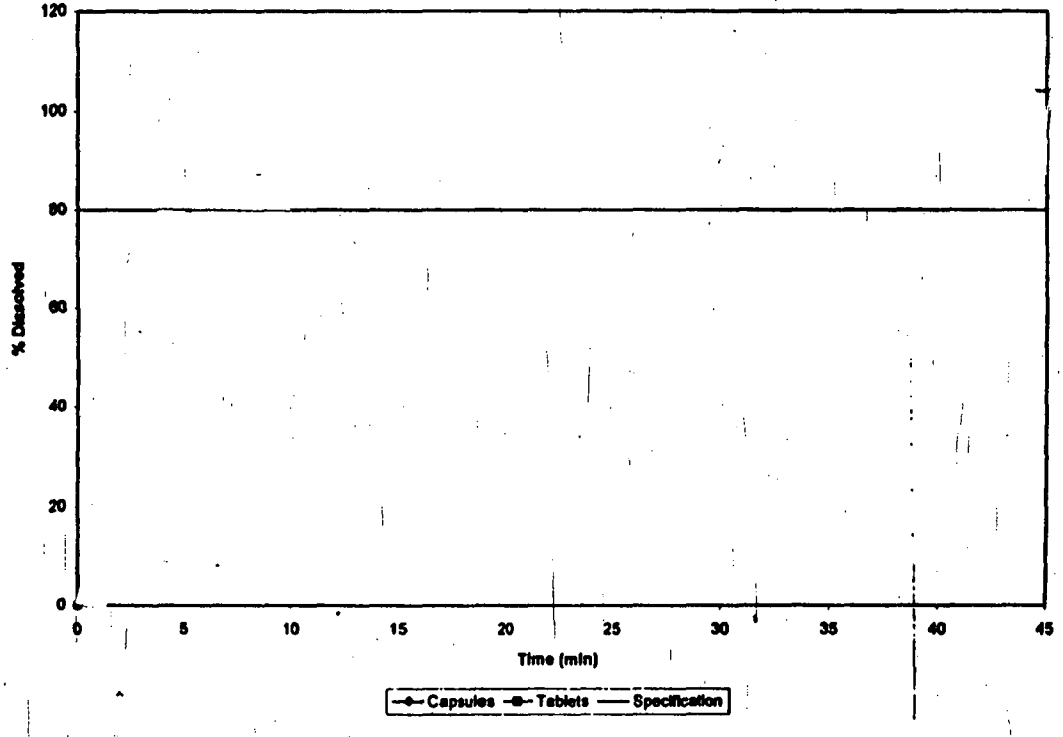
Table II.J.T02 Dissolution Results for BuSpar® 5 mg, Capsule vs. Tablet Forms

BuSpar® 5 mg Capsules, Lot No. 9C18038 (Test Batch), manufactured on 2/17/99 at the Mayagüez, Puerto Rico facility																
Capsule No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10													106	3		
20													106	3		
30													105	3		
45													104	3		
BuSpar® 5 mg Tablets, Lot No. 9D16972 (Reference Batch), manufactured on 3/23/99 at the Mayagüez, Puerto Rico facility																
Tablet No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10													97	4		
20													99	2		
30													99	3		
45													98	3		

II. **Drug Product**

J. Dissolution Comparison (cont.)

Schematic II.J.S01 DissolutionGraph for BuSpar® 5 mg, Capsule vs. Tablet Forms



II. Drug Product

J. Dissolution Comparison (cont.)

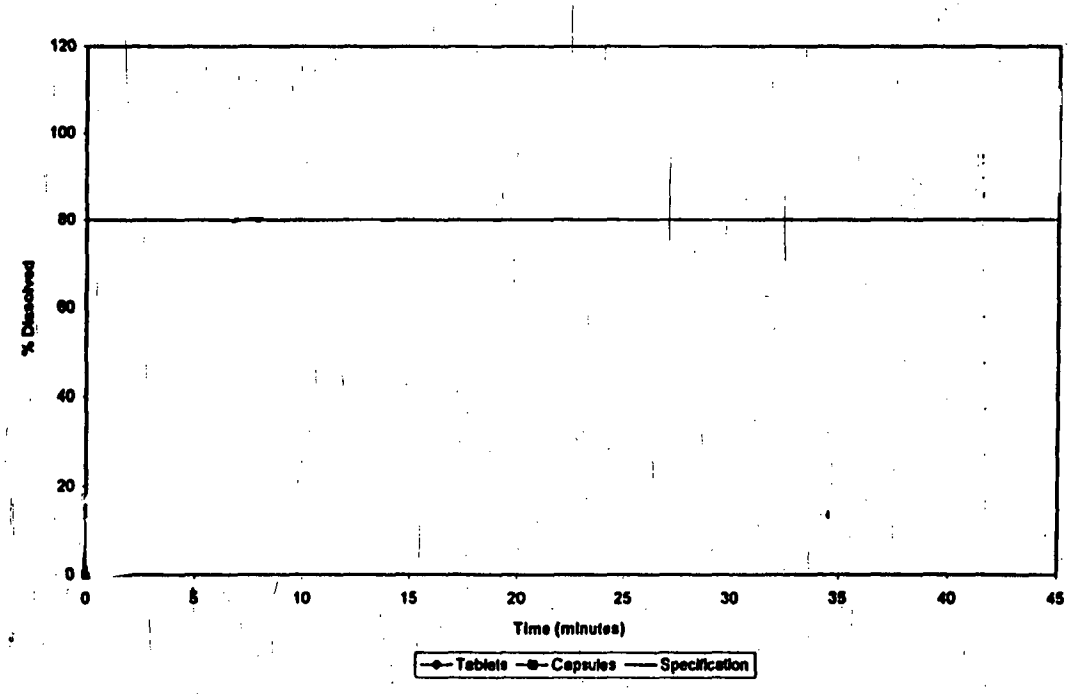
Table II.J.T03 Dissolution Results for BuSpar® 10 mg, Capsule vs. Tablet Forms

BuSpar® 10 mg Capsules, Lot No. 9C14476 (Test Batch), manufactured on 2/17/99 at the Mayagüez, Puerto Rico facility																
Capsule No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10													106	2	109	103
20													106	2		
30													105	2		
45													104	2		
BuSpar® 10 mg Tablets, Lot No. 9F14340 (Reference Batch), manufactured on 6/14/99 at the Mayagüez, Puerto Rico facility																
Tablet No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10													93	2		
20													99	2		
30													99	1		
45													98	2		

II. Drug Product

J. Dissolution Comparison (cont.)

Schematic II.J.S02 DissolutionGraph for BuSpar® 10 mg, Capsule vs. Tablet Forms



II. Drug Product

J. Dissolution Comparison (cont.)

Biobatch

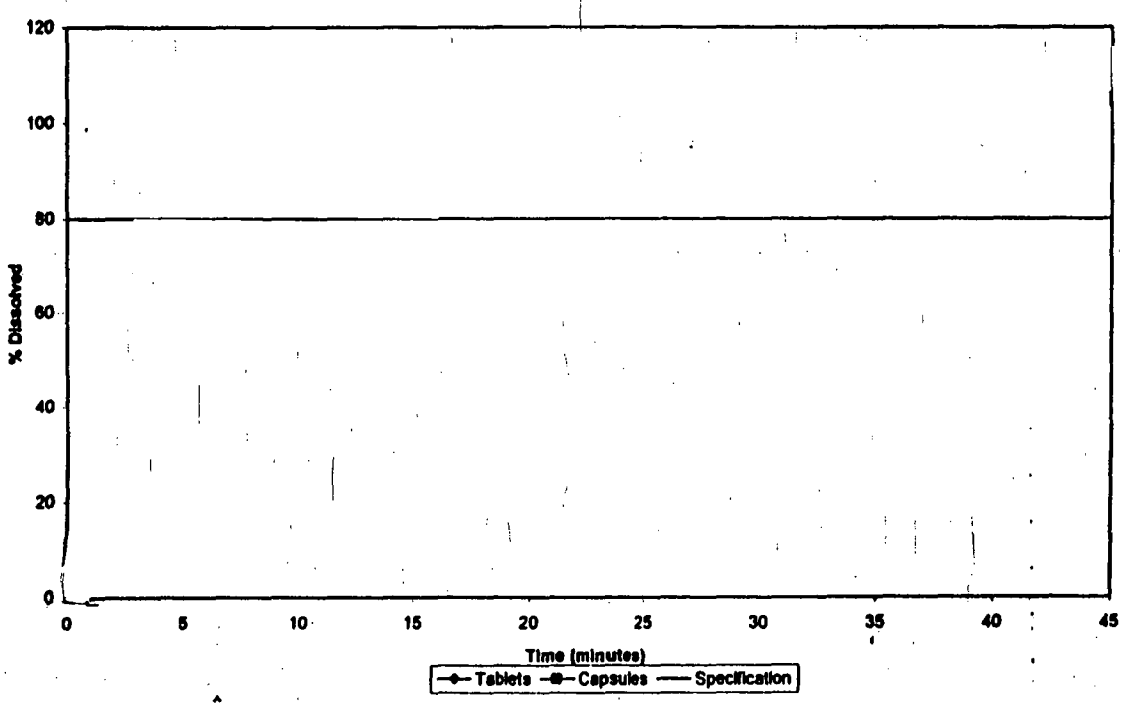
Table II.J.T04 Dissolution Results for BuSpar® 15 mg, Capsule vs. Tablet Forms

BuSpar® 15 mg Capsules, Lot No. 9C13694 (Test Batch), manufactured on 2/17/99 at the Mayagüez, Puerto Rico facility																
Capsule No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10																
20													107	2		
30													106	2		
45													107	2		
													105	2		
BuSpar® 15 mg Tablets, Lot No. A9J096A (Reference Batch), manufactured on 1/21/99 at the Mayagüez, Puerto Rico facility																
Tablet No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10																
20													92	5		
30													103	2		
45													104	2		
													104	2		

II. Drug Product

J. Dissolution Comparison (cont.)

Schematic II.J.S03 DissolutionGraph for BuSpar® 15 mg, Capsule vs. Tablet Forms



II. Drug Product

J. Dissolution Comparison (cont.)

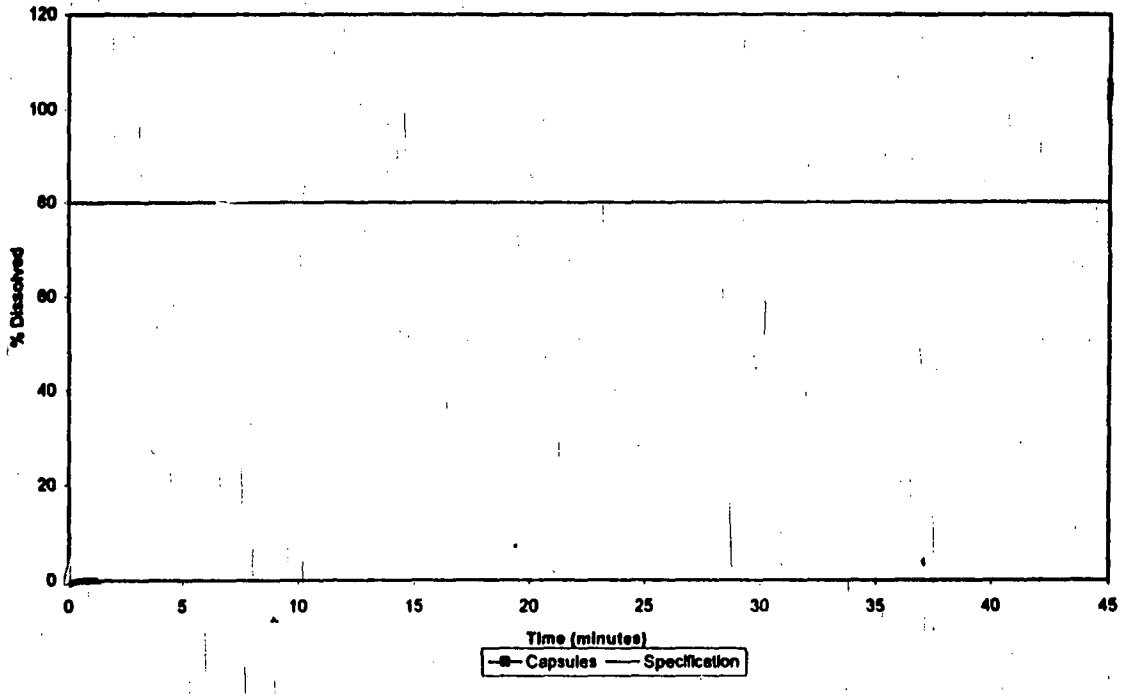
Table II.J.T05 Dissolution Results for BuSpar® 7.5 mg Capsules

BuSpar® 7.5 mg Capsules, Lot No. 9C14482, manufactured on 2/17/99 at the Mayagüez, Puerto Rico facility																
Capsule No.	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Max	Min
Time																
10													104	3		
20													104	3		
30													103	3		
45													102	3		

II. Drug Product

J. Dissolution Comparison (cont.)

Schematic II.J.S04 DissolutionGraph for BuSpar® 7.5 mg Capsules



APPENDIX 4

13 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX 5

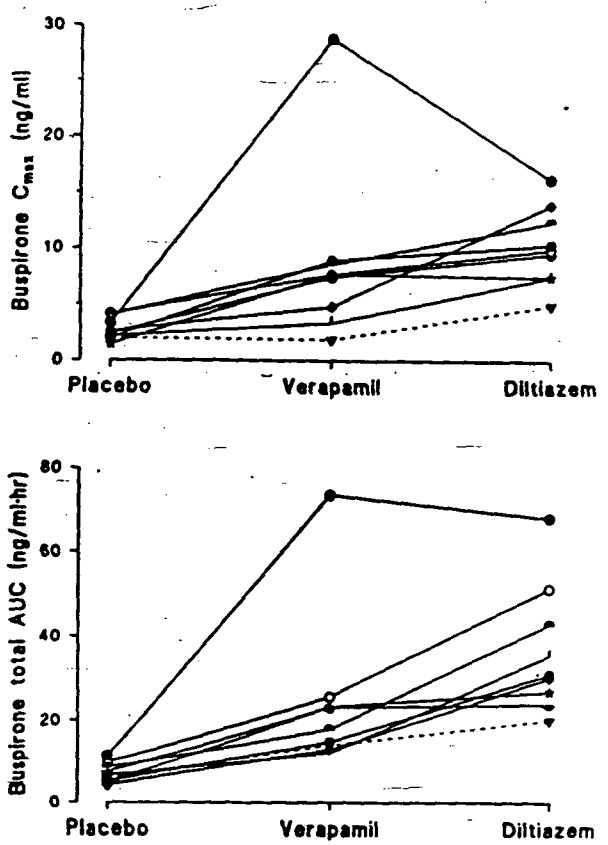


Fig. 2. Individual C_{max} and AUC values of buspirone in nine healthy subjects in placebo, verapamil, and diltiazem phases. *Dashed line* indicates the only female subject (she was using oral contraceptives).

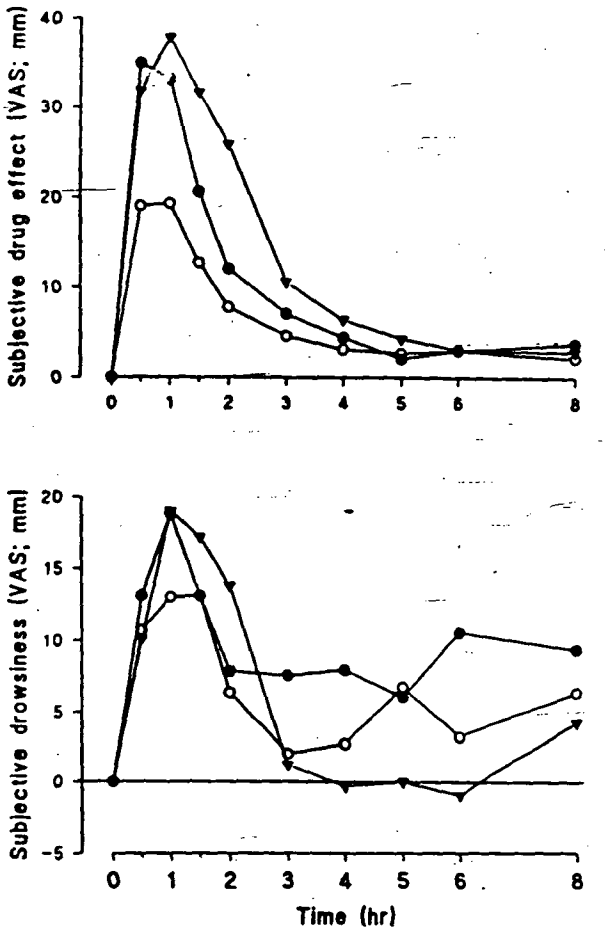


Fig. 3. Upper panel, Subjective drug effect (as millimeters; based on scores from a 100 mm visual analog scale [VAS] and expressed as changes over predose baseline value) after 10 mg oral buspirone and after pretreatment with verapamil (80 mg t.i.d.; *solid circles*), diltiazem (60 mg t.i.d.; *solid triangles*), or placebo *(open circles).* **Lower panel,** Subjective drowsiness (by visual analog scale [VAS]) after verapamil *(solid circles),* diltiazem *(solid triangles),* or placebo *(open circles).* Each point is the mean value for nine subjects at the corresponding time; error bars have been omitted for clarity.

AUC(1-19) or C_{max} of verapamil and the ratio of the AUC(0-∞) of buspirone in the verapamil phase to the AUC(0-∞) of buspirone in the placebo phase. Similarly, the correlations between the AUC(1-19) or C_{max} of diltiazem and the corresponding buspirone AUC ratio were not significant.

Pharmacodynamics. The results of the pharmacodynamic tests are shown in Fig. 3 and Table II. The subjective overall drug effect showed a significant difference between the verapamil and placebo phases ($p < 0.05$) and between the diltiazem and placebo phases ($p < 0.05$). There were no other significant differences between the placebo and verapamil or diltiazem phases in the pharmacodynamic tests. Side effects of buspirone were reported more often in the verapamil (five subjects) and diltiazem (nine subjects) phases than in the placebo phase (two subjects), with the difference between diltiazem and placebo being statistically significant ($p < 0.05$ by the McNemar test). The side effects resolved spontaneously within 1 to 3 hours in each case and none of the subjects discontinued the study because of side effects.

DISCUSSION

This study shows a threefold and sixfold increase in the total AUC of buspirone in healthy volunteers after five doses of verapamil or diltiazem, respectively, with the effect of diltiazem being significantly greater than that of verapamil. The C_{max} of buspirone was affected by verapamil and diltiazem to the same extent as the

Table II. Results of pharmacodynamic tests presented as incremental or decremental AUC values after 10 mg oral buspirone, given 1 hour after fifth (last) dose of pretreatment with placebo, verapamil (80 mg), or diltiazem (60 mg) three times a day in nine healthy volunteers

Test	*Variable*	*Placebo (control)*	*Verapamil phase*	*Diltiazem phase*
DSST	AUC(0-4) (digits · hr)	20.6 ± 25.9	32.9 ± 38.5	34.6 ± 35.9
	AUC(0-8) (digits · hr)	40.2 ± 51.9	71.4 ± 73.9	59.0 ± 71.8
CFFT	AUC(0-4) (Hz · hr)	2.5 ± 2.4	4.2 ± 2.1	5.9 ± 4.3
	AUC(0-8) (Hz · hr)	5.9 ± 4.5	7.8 ± 6.3	10.9 ± 8.4
Drowsiness (VAS)	AUC(0-4) (mm · hr)	26.6 ± 26.0	40.0 ± 42.9	34.6 ± 50.9
	AUC(0-8) (mm · hr)	45.9 ± 61.7	79.6 ± 125	37.3 ± 130
Drug effect (VAS)	AUC(0-4) (mm · hr)	37.4 ± 25.9	62.6 ± 28.3*	83.7 ± 18.8†
	AUC(0-8) (mm · hr)	48.4 ± 35.1	77.3 ± 49.0	98.8 ± 30.8*
Sway, eyes open	AUC(0-4) (mm/min · hr)	77.3 ± 140	57.1 ± 135	10.3 ± 155
	AUC(0-8) (mm/min · hr)	107 ± 276	90.7 ± 204	5.8 ± 325
Sway, eyes closed	AUC(0-4) (mm/min · hr)	−171 ± 324	−170 ± 404	55 ± 269
	AUC(0-8) (mm/min · hr)	−420 ± 656	−446 ± 753	17 ± 466

Data are mean values ± SD. DSST, Digit Symbol Substitution test; CFFT, Critical Flicker Fusion test; VAS, visual analog scale; AUC, area under the effect versus time curve above (drowsiness, drug effect, sway) or below (DSST, CFFT) baseline from 0 to 4 hours or from 0 to 8 hours.
*$p < 0.05$ versus placebo phase.
†$p < 0.01$ versus placebo phase.

total AUC. A considerable between-subject variability was evident in the extent of both interactions. Although the only female subject in the study seemed to have a smaller interaction than the male subjects (she also used oral contraceptives), no conclusions regarding possible gender-related differences or role of oral contraceptive steroids can be drawn from this study. The pharmacokinetic interactions were associated with only minor impairment of psychomotor performance; however, an increased frequency of side effects was observed after buspirone in the diltiazem phase.

Buspirone has been reported to undergo oxidative metabolism in the liver,[16-18] but the specific CYP enzymes involved in its biotransformation in human beings remain to be identified. However, several lines of evidence strongly suggest that CYP3A4, which is abundantly expressed not only in the liver but also in the gut wall,[19-21] plays a major role in the presystemic metabolism of buspirone. First, like many substrates of CYP3A4, buspirone also undergoes extensive first-pass metabolism, resulting in a bioavailability of about 5%.[6] Second, two prototype CYP3A4 inhibitors, erythromycin and itraconazole, have been shown to greatly increase plasma buspirone concentrations.[7] Finally, in the present study, verapamil and diltiazem, both known inhibitors of CYP3A4,[10,11] considerably increased the C_{max} and AUC of buspirone.

The elimination $t_{½}$ of buspirone was not affected by either verapamil or diltiazem. Because it is not likely that the volume of distribution of buspirone would have been altered by verapamil or diltiazem, these data seem to indicate that the systemic clearance of buspirone remains largely unchanged by verapamil and diltiazem. It is therefore reasonable to assume that the interaction of buspirone with verapamil and diltiazem resulted almost solely from inhibition of the (CYP3A4-mediated) first-pass metabolism of buspirone in the gut wall and liver. However, both verapamil and diltiazem may increase hepatic blood flow,[22] and the possibility that this effect could contribute to the reduction of first-pass metabolism of buspirone cannot be excluded.

Diltiazem has been shown to increase the AUC of orally administered midazolam[10] and triazolam[11] nearly to the same extent as that of buspirone in the present study. However, unlike the $t_{½}$ of buspirone, the $t_{½}$ values of midazolam and triazolam were significantly prolonged by diltiazem.[10,11]

With the exception of the overall drug effect and frequency of side effects, no significant differences between verapamil or diltiazem and placebo were observed in the pharmacodynamics of buspirone. Similarly, the effects of 10 mg buspirone were relatively modest in our previous study despite the very high buspirone concentrations caused by itraconazole.[7]

The intensity of a pharmacologic response is proportional to the logarithm of the drug concentration. Accordingly, the present interactions were more pronounced in the pharmacokinetics than in the pharmacodynamics of buspirone. Furthermore, buspirone causes less sedation and impairment of psychomotor performance than benzodiazepines.[2-5] The pharmacodynamic effects of benzodiazepines may therefore be better

reflected in the classic psychomotor tests than those of buspirone. Accordingly, the overall drug effect was the only pharmacodynamic variable showing increased effects of buspirone after verapamil or diltiazem.

In conclusion, verapamil and diltiazem considerably increased plasma buspirone concentrations. Although the clinical significance of these interactions is not clear from the present study, they may predispose to increased side effects of buspirone. Buspirone should therefore be used with caution in patients taking verapamil, diltiazem, or other inhibitors of CYP3A4.

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References

1. Goa KL, Ward A. Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs 1986;32:114-29.
2. Bond AJ, Lader MH. Comparative effects of diazepam and buspirone on subjective feelings, psychological tests and the EEG. Int Pharmacopsychiatry 1981;16:212-20.
3. Bond A, Lader M, Shrotriya R. Comparative effects of a repeated dose regime of diazepam and buspirone on subjective ratings, psychological tests and the EEG. Eur J Clin Pharmacol 1983;24:463-7.
4. Erwin CW, Linnoila M, Hartwell J, Erwin A, Guthrie S. Effects of buspirone and diazepam, alone and in combination with alcohol, on skilled performance and evoked potentials. J Clin Psychopharmacol 1986;6:199-209.
5. Greenblatt DJ, Harmatz JS, Gouthro TA, Locke J, Shader RI. Distinguishing a benzodiazepine agonist (triazolam) from a nonagonist anxiolytic (buspirone) by electroencephalography: kinetic-dynamic studies. Clin Pharmacol Ther 1994;56:100-11.
6. Mayol RF, Adamson DS, Gammans RE, LaBudde JA. Pharmacokinetics and disposition of ^{14}C-buspirone HCl after intravenous and oral dosing in man [abstract]. Clin Pharmacol Ther 1985;37:210.
7. Kivistö KT, Lamberg TS, Kantola T, Neuvonen PJ. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. Clin Pharmacol Ther 1997;62:348-54.
8. Schlanz KD, Myre SA, Bottorff MB. Pharmacokinetic interactions with calcium channel antagonists: part I. Clin Pharmacokinet 1991;21:344-56.
9. Schlanz KD, Myre SA, Bottorff MB. Pharmacokinetic interactions with calcium channel antagonists: part II. Clin Pharmacokinet 1991;21:448-60.
10. Backman JT, Olkkola KT, Aranko K, Himberg JJ, Neuvonen PJ. Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol 1994;37:221-5.
11. Varhe A, Olkkola KT, Neuvonen PJ. Diltiazem enhances the effects of triazolam by inhibiting its metabolism. Clin Pharmacol Ther 1996;59:369-75.
12. Gaillard Y, Gay-Montchamp JP, Ollagnier M. Simultaneous screening and quantitation of alpidem, zolpidem, buspirone and benzodiazepines by dual-channel gas chromatography using electron capture and nitrogen-phosphorous detection after solid-phase extraction. J Chromatogr 1993;622:197-208.
13. Dube LM, Mousseau N, McGilveray IJ. High-performance liquid chromatographic determination of diltiazem and four of its metabolites in plasma: evaluation of their stability. J Chromatogr 1988;430:103-11.
14. Hynning PÅ, Anderson P, Bondersson U, Boreus LO. Liquid-chromatographic quantification compared with gas-chromatographic mass-spectrometric determination of verapamil and norverapamil in plasma. Clin Chem 1988;34:2502-3.
15. Backman JT, Olkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther 1996;59:7-13.
16. Gammans RE, Mayol RF, LaBudde JA. Metabolism and disposition of buspirone. Am J Med 1986;80(suppl 3B):41-51.
17. Jajoo HK, Mayol RF, LaBudde JA, Blair IA. Metabolism of the antianxiety drug buspirone in human subjects. Drug Metab Dispos 1989;17:634-40.
18. Jajoo HK, Blair IA, Klunk LJ, Mayol RF. In vitro metabolism of the antianxiety drug buspirone as a predictor of its metabolism in vivo. Xenobiotica 1990;20:779-86.
19. Kolars JC, Schmiedlin-Ren P, Schuetz JD, Fang C, Watkins PB. Identification of rifampicin-inducible P450IIIA4 (CYP3A4) in human small bowel enterocytes. J Clin Invest 1992;90:1871-8.
20. Lown KS, Kolars JC, Thummel KE, Barnett JL, Kunze KL, Wrighton SA, et al. Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Drug Metab Dispos 1994;22:947-55.
21. Kivistö KT, Bookjans G, Fromm MF, Griese EU, Münzel P, Kroemer HK. Expression of CYP3A4, CYP3A5 and CYP3A7 in human duodenal tissue. Br J Clin Pharmacol 1996;42:387-9.
22. Bauer LA, Stenwall M, Horn JR, Davis R, Opheim K, Greene L. Changes in antipyrine and indocyanine green kinetics during nifedipine, verapamil and diltiazem therapy. Clin Pharmacol Ther 1986;40:239-42.

Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone

Background: Buspirone has an extensive first-pass metabolism, which makes it potentially susceptible to drug interactions. The aim of this study was to investigate possible interactions of buspirone with verapamil and diltiazem.

Methods: In a randomized, placebo-controlled, three-phase crossover study, nine healthy volunteers received either 80 mg verapamil, 60 mg diltiazem, or placebo orally three times a day. On day 2, after the fifth dose, 10 mg buspirone was given orally. Plasma concentrations of buspirone, verapamil, and diltiazem were determined up to 18 hours, and the effects of buspirone were measured up to 8 hours.

Results: Verapamil and diltiazem increased the area under the buspirone plasma concentration–time curve [AUC (0-∞)] 3.4-fold ($p < 0.001$) and 5.5-fold ($p < 0.001$), respectively. The peak plasma concentration of buspirone was increased 3.4-fold ($p < 0.001$) and 4.1-fold ($p < 0.001$) by verapamil and diltiazem, respectively. The effect of diltiazem on the AUC(0-∞) of buspirone was significantly ($p < 0.05$) greater than that of verapamil. The elimination half-life of buspirone was not changed by verapamil and diltiazem. Of the six pharmacodynamic variables, only the subjective overall drug effect of buspirone was significantly increased with verapamil ($p < 0.05$) and diltiazem ($p < 0.05$). Side effects of buspirone occurred more often ($p < 0.05$) with diltiazem than with placebo.

Conclusions: Both verapamil and diltiazem considerably increase plasma buspirone concentrations, probably by inhibiting its CYP3A4-mediated first-pass metabolism. Thus enhanced effects and side effects of buspirone are possible when it is used with verapamil, diltiazem, or other inhibitors of CYP3A4. (Clin Pharmacol Ther 1998;63:640-5.)

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Buspirone is an azapirone anxiolytic agent[1] that causes less sedation and impairment of psychomotor performance than benzodiazepines.[2-5] After an oral dose, buspirone is almost totally absorbed, but its oral bioavailability is only about 5% because of extensive metabolism during the first pass.[6] The specific CYP enzymes involved in the biotransformation of buspirone are not currently known. However, itraconazole and erythromycin, which are potent CYP3A4 inhibitors, increased the total area under the concentration–time curve (AUC) of buspirone 19-fold and 6-fold, respectively.[7]

The calcium-channel blocking agents verapamil and diltiazem are inhibitors of CYP3A4 and they can increase plasma concentrations of, for example, orally administered triazolam, midazolam, and cyclosporine (INN, ciclosporin).[8-11] Because buspirone seems to be susceptible to interactions with CYP3A4 inhibitors, we wanted to investigate the effects of these calcium channel blocking agents on the plasma concentrations and effects of buspirone in healthy volunteers.

MATERIAL AND METHODS

Subjects. Nine healthy volunteers (eight men and one woman; age range, 22 to 26 years; weight range, 55 to 92 kg) participated in this study. All subjects were

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considered to be healthy on the basis of medical history, physical examination, electrocardiographic findings, and routine laboratory tests before entering the study. None of the subjects used any other medication during the study, except for one woman who was using oral contraceptive steroids (20 μg ethinyl estradiol [INN, ethinylestradiol] plus 150 μg desogestrel). All volunteers gave their written informed consent.

Study design. The study protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and the Finnish National Agency for Medicines. A randomized, placebo-controlled, crossover study design with three phases was used. The phases were separated by 2-week washout periods. The subjects received five doses in total of 80 mg verapamil (80 mg Verpamil tablet, Orion Ltd., Espoo, Finland), 60 mg diltiazem (60 mg Dilzem tablet, Orion Ltd.), or placebo orally three times a day (at 8 AM, 1 PM, and 8 PM). On day 2, each subject was administered a single 10 mg oral dose of buspirone (one 10 mg Buspar tablet, Bristol-Myers Squibb, Espoo, Finland) with 150 ml water at 2 PM (i.e., 1 hour after the last dose of pretreatment). The volunteers fasted for 2 hours before buspirone intake and had standard meals 3 and 6 hours after buspirone administration. The use of alcohol, coffee, tea, cola, and grapefruit juice was not allowed during the test days; tobacco was also forbidden.

Blood sampling and determination of plasma drug concentrations. On day 2, a forearm vein in each volunteer was cannulated and timed blood samples (10 ml each) were drawn into tubes that contained ethylenediaminetetraacetic acid before buspirone administration and ½, 1, 1½, 2, 3, 4, 5, 6, 8, and 18 hours later. Plasma was separated within 30 minutes, divided into three tubes, and stored at –40° C until analysis of drug concentrations. Plasma buspirone concentrations were determined by use of a capillary gas chromatographic method involving solid-phase extraction and nitrogen-phosphorous detection.[12] Zolpidem was used as an internal standard. The limit of quantification was 0.1 ng/ml. The between-day coefficient of variation was 2.8% at 2.3 ng/ml ($n = 9$). Plasma verapamil and diltiazem concentrations were determined by HPLC as described previously.[13,14] The limit of quantification was 2.0 ng/ml for verapamil and 5.0 ng/ml for diltiazem. The between-day coefficient of variation was 6.5% at 19.0 ng/ml ($n = 9$) for verapamil and 4.0% at 24.7 ng/ml ($n = 6$) for diltiazem.

Pharmacokinetics. The pharmacokinetics of buspirone were characterized by the peak plasma concentration (C_{max}), time to C_{max} (t_{max}), AUC(0-8) and AUC(0-∞), and elimination half-life ($t_{½}$). The terminal

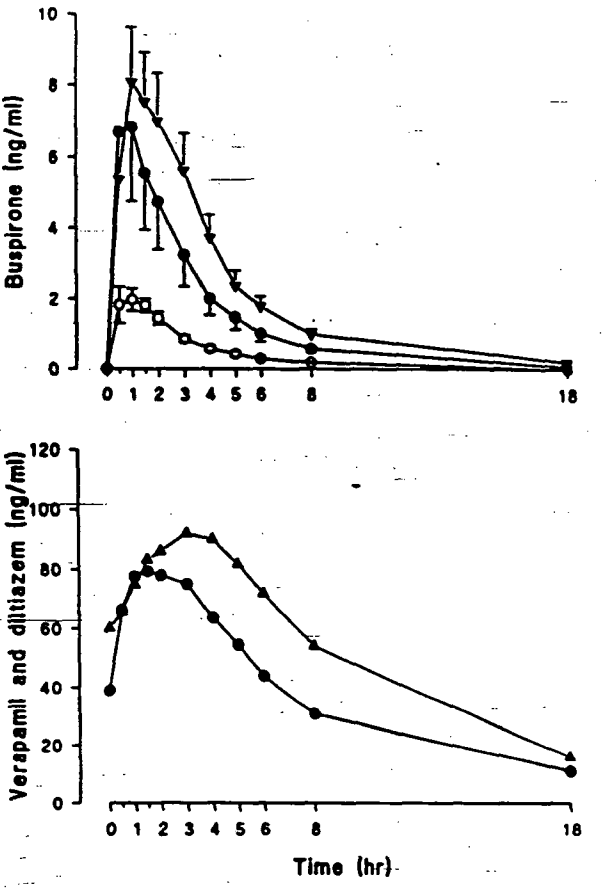

Fig. 1. **Upper panel,** Plasma concentrations of buspirone in nine healthy subjects (mean ± SE) after 10 mg oral buspirone and after oral pretreatment with verapamil (80 mg t.i.d.; *solid circles*), diltiazem (60 mg t.i.d.; *solid triangles*), or placebo *(open circles).* **Lower panel,** Plasma concentrations of verapamil *(solid circles)* and diltiazem *(solid triangles)* in nine healthy subjects on day 2. Time 0 refers to the administration of buspirone (i.e., 1 hour after the last [fifth] dose of verapamil or diltiazem). Error bars were omitted for clarity.

log-linear phase of the plasma-buspirone concentration–time curve was identified visually for each subject, and the elimination rate constant (k_e) was determined by a linear regression analysis, with use of the last three to five points of the plasma concentration–time curve. The elimination $t_{½}$ was calculated from the equation:

$$\text{Elimination } t_{½} = \ln 2/k_e$$

The AUC values were calculated by the linear trapezoidal rule, with extrapolation to infinity by dividing the last measured concentration by k_e. The pharmacokinetics of verapamil and diltiazem on day 2 were char-

Table I. Pharmacokinetic variables of 10 mg oral buspirone, given 1 hour after the fifth (last) dose of pretreatment with placebo, verapamil (80 mg), or diltiazem (60 mg) three times a day in nine healthy volunteers

Variable	*Placebo (control)*	*Verapamil phase*	*Diltiazem phase*
C_{max} (ng/ml)	2.6 ± 1.0	8.8 ± 7.9*	10.3 ± 3.5*
Relative to control	1	3.4	4.1
t_{max} (hr)‡ (0.5-1.5)	1 (0.5-5)	1 (0.5-3)	
Elimination $t_{½}$ (hr)	2.4 ± 0.6	2.6 ± 1.0	3.3 ± 1.3
Relative to control	1	1.2	1.4
AUC(0-8) (ng/ml · hr)	6.3 ± 2.3	21.8 ± 18.7*	31.1 ± 14.2*
Relative to control	1	3.3	5.0
AUC(0-∞) (ng/ml · hr)	6.9 ± 2.5	24.3 ± 19.2*	36.8 ± 15.2*†
Relative to control	1	3.4	5.5

Data are mean values ± SD; ‡t_{max} data are given as the median, with the range in parentheses.
C_{max}, Peak plasma concentration; t_{max}, time to reach C_{max}; $t_{½}$, half-life; AUC(0-8), area under the buspirone plasma concentration–time curve from 0 to 8 hours; AUC(0-∞), area under the buspirone plasma concentration–time curve from zero to infinity.
*$p < 0.001$ versus placebo phase.
†$p < 0.05$ versus verapamil phase.

acterized by C_{max} and AUC(1-19), that is, the AUC from 1 hour after the last dose of verapamil or diltiazem up to 19 hours.

Pharmacodynamic measurements. The pharmacodynamic effects of buspirone were measured immediately after each blood sampling (up to 8 hours) by six tests.[15] The volunteers had been trained to properly perform the tests before the study began. In the Digit Symbol Substitution test, the number of digits correctly substituted in 2 minutes was calculated. In the Critical Flicker Fusion test, the frequency (hertz) at which a flickering red light gave an impression of a constant light was measured. Horizontal, 100 mm long visual analog scales were used to measure subjective drowsiness and subjective overall drug effect. In the postural sway test, the mean speed (in millimeters per minute) of the subject's mass center was measured. The speed was recorded for 30 seconds with eyes open and thereafter 30 seconds with eyes closed, with use of a swaymeter (Erikois-Elektroniikka Ltd., Orimattila, Finland). For each pharmacodynamic variable, the incremental (drowsiness, overall drug effect, and postural sway) or decremental (Digit Symbol Substitution test and Critical Flicker Fusion test) area under the effect versus time curve (i.e., area above or below baseline) from 0 to 4 hours [AUC(0-4)] and from 0 to 8 hours [AUC(0-8)] was calculated by the linear trapezoidal rule. The volunteers were asked about possible side effects of buspirone 1, 2, and 3 hours after buspirone administration.

Statistical analysis. Results are given as mean values ± SD, or, in the case of t_{max}, as median with range. The pharmacokinetic variables of buspirone and the AUC(0-4) and AUC(0-8) values for the pharmacodynamic variables between the three phases were compared with a one-way ANOVA, with the Tukey test used for post hoc comparisons. The Wilcoxon test was used for analysis of t_{max} data. The level of statistical significance was $p < 0.05$. The statistical program Systat for Windows, version 6.0.1 (SPSS Inc., Chicago, Ill.) was used for statistical analysis.

RESULTS

Pharmacokinetics of buspirone. Verapamil and diltiazem considerably increased plasma buspirone concentrations. Verapamil increased both the mean AUC(0-∞) and C_{max} of buspirone 3.4-fold ($p < 0.001$) compared with placebo (Fig. 1; Table I). After diltiazem administration, the mean buspirone AUC(0-∞) and C_{max} values were increased 5.5-fold ($p < 0.001$) and 4.1-fold ($p < 0.001$), respectively (Fig. 1; Table I). The AUC(0-∞) of buspirone was significantly ($p < 0.05$) greater in the diltiazem phase than in the verapamil phase. The elimination $t_{½}$ and t_{max} of buspirone were not significantly affected by either verapamil or diltiazem. There were considerable between-subject differences in the extent of both interactions (Fig. 2). For example, the increase of the AUC(0-∞) of buspirone ranged from 1.9-fold to 6.4-fold in the case of verapamil and from 3.3-fold to 7.4-fold in the case of diltiazem. The extent of the interaction in the only female subject who used oral contraceptives was, if anything, smaller than that in the other (male) subjects (Fig. 2).

Concentrations of verapamil and diltiazem. The AUC(1-19) values for verapamil and diltiazem varied 4.2-fold and 3.1-fold between individual volunteers, respectively. There was no significant correlation between the