N 18730

NDA

18-730

Approval

Letter

MAY - 4 1984

NDA 18-730

Fredrick J. Shainfeld, Pharm. D.
Vice President
Director, Regulatory Affairs
Zenith Laboratories, Inc.
140 LeGrand Avenue
Northvale, New Jersey 07647

Gentlemen:

We acknowledge the receipt on April 13, 1984 of your communication dated April 12 ,1984 enclosing final printed labeling pursuant to your new drug application for indomethacin capsules 25mg and 50mg.

We also acknowledge receipt of your additional communications dated July 13, August 31, September 13, September 28, 1983, March 7, April 25, and May 1, 1984.

The application was filed on April 13, 1984.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application. This approval covers only Fabbrica Italiana Sintetici as the supplier of the new drug substance. The approval is also conditional upon the following commitments which were agreed upon in a telephone conversation on May 3, 1984 between Dr. R. H. Wood of this Administration and Mr. Kenneth Larson and Dr. Fredrick Shainfeld of Zenith Laboratories:

(1) Concerning the stability studies, (a) current stability studies will continue and the first three production lots of each package size and strength will be placed on stability study, (b) the data will be submitted promptly to the FDA as it becomes available, and (c) any lot failing the NDA specifications will be promptly withdrawn from the market;

(2) For the two degradation reference standards, certificates of analysis will be submitted as well as a full description of the methods of analysis.

(3) Since validation of the methods has not been completed by the FDA laboratories, a commitment has been made to cooperate with the FDA in accomplishing the validation and to revise the methods if necessary.

Please submit one market package of the drug when available.

At the next printing the package insert should be revised as follows:

Under INDICATIONS, first paragraph after the numbered [redacted]ications, last sentence, the word "adverse" should be inserted [redacted] words "possible" and "effects".

Please submit copies of the introductory promotional material for this product. Copies should be submitted with a cover letter to both the Director, Division of Oncology and Radiopharmaceutical Drug Products (HFN-150) and to the Director, Division of Drug Advertising and Labeling (HFN-240).

Sincerely yours,

John F. Palmer, M.D.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Center for Drugs and Biologics

Enclosures: Records and Reports Requirements (Reg. 311.300)
Conditions of Approval of an NDA

cc:
[redacted]
NDA 18-730 orig.
HFN-150/Div. File
HFN-150/Mr. Behrens
HFN-150/Dr. Ochota
HFN-150/Dr. Chen
HFN-150/Mr. Huckins
HFN-150/Dr. Wood
HFN-616
HFL-10

Drafted:HTBehrens:4-18-84
R/D endorsed:Mr. Huckins:4-18-84
Dr. Richman:4-18-84
Mr. Scully:5-4-84
Dr. Jerussi:5-4-84
Dr. Palmer:5-4-84
Revised:RHWood:5-4-84
Revised:RAJerussi:5-4-84
Typed:sm:5-4-84:2258P

NDA APPROVAL

Pharm.

JUN 30 1982

REVIEW AND EVALUATION OF PHARMACOLOGY
AND TOXICOLOGY DATA
Date of Submission: 1-15-82
Date of Review: 6-8-82

NDA: 18730
Sponsor: Zenith Laboratories, Inc., Northvale, New Jersey 07647
Drug: Indomethacin Capsules, 25 mg. and 50 mg.
Category: Non-steroidal anti-inflammatory
Components: Indomethacin, USP

Related To:
Indications and Dosage:
Rheumatoid arthritis, ankylosing spondylilitis and acute gouty arthritis 25 mg. bid to 50 mg. tid (daily dose should not exceed 200 mg.).

Preclinical Study:
Of the 53 references cited in support of the "safety" of indomethacin, only 5 articles pertained to the animal studies. No other preclinical studies have been submitted in this NDA.

Evaluation and Comment:
Indocin (Indomethacin, Merck Sharp & Dohme) is a marketed drug. In NDA 18730 the sponsor has submitted the result from the bioavailability study in order to establish the bioequivalency of his products, Indomethacin Capsules 25 mg. and 50 mg., and Indocin 50 mg. No other clinical or preclinical studies were submitted. Only a few published animal studies were cited in the list of the reference articles.

Recommendation:
In the addendum to a memo dated June 5, 1981, regarding "clinical and preclinical data and review requirements for paper NDA", Dr. Finkel stated: (----if no preclinical animal data is submitted or cited the pharmacology review should) state that the clinical data submitted plus knowledge of the adverse effects and safety of the drug in clinical use obviate the need for submittal of such (preclinical) data. Since indomethacin has been used clinically for many years and its adverse effects and safety have been well-established, there is no objection to the approval of this NDA from the view point of pharmacology.

Conrad H. Chen

Conrad H. Chen, Ph.D.

Addendum: If considered a "paper NOA", my understanding based on conversations with Dr. Vera Glocklin HFO-102, is that no toxicity studies need be conducted by an applicant. Thus, if a suitable package insert is submitted, it would appear that the application would be considered approvable by pharmacology.

David J. Richman, Ph.D.

cc:
Orig NDA 18-730
HFD-150, HFD-180
HFD-150/CHChen:6/8/82
HFD-150/CSO/RPodliska
R/D endorsed by DJRichman:6/11/82
F/T DAlvarez:6/18/82:Wang 8395

Chem.

NDA #: 18730

Applicant: Zenith Laboratories Inc.
Sponsor:
Address: Northvale, N.J. 07647

Division: HFN-150
Chemist Review #: 7
Reviewing Chemist: Robert N. Huchins
Date Completed: 5/2/84

MAY 4 - 1984

Product Name(s):
Proprietary:
Non-proprietary: Indomethacin
Compendium:
USAN:
Code name/number:

FINISHED REVIEW
R.A. Jenni 5/4/84

Dosage Form(s) and Route(s) of Administration: oral, capsules, 25 and 50 mg

Pharmacological Category and/or Principal Indication: anti-inflammatory agent

Structural Formula & Chemical Name:

Initial Submission: January 15, 1982
Amendment(s): April 24, 1984
Related Documents: April 25, 1984 (2)
April 30, 1984
May 1, 1984

Remarks: The new HPLC assay for impurities has been validated by Zenith for system suitability and sensitivity. The method is ready for validation by FDA Labs. The impurity standards for the two degradation products have been submitted but the assay was not submitted so not know if method is specific. Also we asked for cert. of analysis.
There is a question on the stability data that Zenith has submitted in support of their proposed expiration dating of 24 months for 25mg and 50mg capsules in 100's, 500's and 1000's. To ~~25mg~~ they have data for only one lot for each strength ~~capsule~~ to cover the 24 month dating for the ~~pack~~ 100's and 1000's ~~packages~~. They have 2 lots of each size on stability but only 3 months of satisfactory data. Unable to get commitment to withdraw from market any lot that fails to meet NDA approved specifications.

Conclusions and Recommendations: The application is approvable - see draft of Chemist's portion of NDA letter

Robert N. Huchins
Chemist

cc: IND/NDA Orig. 18-730
~~HFD-102/Kumkumian (Only Chemist's Review #1's)~~
~~HFD~~ Division File 150
HFD-Div/drafter/date/typist/date

R/D initialed by R. Huchins 150
R.Wood 150

RAWood 5/3/84

RA Jenni 5/4/84

MOR

MEDICAL OFFICER REVIEW OF NDA 18-730

MAR 29 1982

Original Submission, dated January 15, 1982;
Received by me February 22, 1982;
Reviewed by me February 26, 1982

SPONSOR: Zenith Laboratories, Inc.
140 LeGrand Avenue
Northvale, NJ 07647

I. NAME OF THE DRUG PRODUCT

A. USAN: indomethacin.

B. Trademark: not given.

C. Therapeutic Claim: antiphlogistic.

D. Forms available: 25 mg and 50 mg capsules.

II. BIOEQUIVALENCE STUDY

21 fasting, normal, healthy male volunteers, 11 Caucasoid, 10 Negroid, age 19 to 37, mean 27.6 years, received in a three-way crossover design 25 mg Zenith indomethacin capsule, 50 mg Zenith indomethacin capsule, and 50 mg MSD Indocin capsule.

Blood samples were drawn at baseline and 14 times over 36 hours thereafter; all urine excreted over 36 hours after dosing was collected as a single pooled sample.

Results

AUC for 25 mg indomethacin Zenith was 9,564, compared to 9,154 for Indocin with 8.85% confidence interval, indicating with 95% confidence that Zenith indomethacin is within this percent of value for Indocin.

AUC for 50 mg indomethacin Zenith was 9,620, compared to 9,154 for Indocin with 5.12% confidence interval.

Remark:

This study is to be reviewed by HFD-522. (N.B.: No safety problems have been encountered in this study.)

III . DATA FROM MEDICAL LITERATURE

III'. EFFECTIVENESS

A. V. Wright et al. Indomethacin in the treatment of rheumatoid arthritis. Ann Rheum Dis 28:157-162, 1969: randomized, double-masked and crossover study divided into three 4-week periods in which 24 patients with definite R.A. received 150 mg per day of indomethacin, 300 mg phenylbutazone daily. placebo.

Results

"A comparison of the three treatments revealed significant improvement in both active treatment groups in pain relief and aspirin intake when compared to the placebo. Phenylbutazone was significantly better than placebo in relief of morning stiffness and in grip strength and was not significantly different from indomethacin.

Three patients required dosage reduction because of indomethacin side effects. Minor central nervous system and gastrointestinal side effects were reported with indomethacin."

B. R. Pinals et al. Relative efficacy of indomethacin and acetylsalicylic acid in rheumatoid arthritis, [illegible] 276:512-514, 1967:

randomized, double-masked and crossover study of 24 adult patients with definite or classical R.A., 13F, 11M, in which the patients received for one month from 50 to 200 mg daily indomethacin, and from 1.6 to 6.4 g aspirin daily.

Results:

"Three of the 24 patients did not complete the study: one patient because of other medical complications, one because of indomethacin side effects, and one because of ASA side effects. In the remaining 21 patients there was no significant difference between the two medications in either subjective or objective criteria."

"Both drugs produced a similar frequency of side effects; there were no qualitative differences: ASA produced more tinnitus and deafness, indomethacin more headaches. The incidences of gastrointestinal side effects were similar."

C. J. Castles et al. Multicenter comparison of naproxen and indomethacin in rheumatoid arthritis. Arch Int Med 138: 362-6, 1978:

132 adult patients of both sexes with definite or classical R.A. entered the 16 week, randomized, double-masked and double-crossover study with each patient assigned to one of the six possible sequences of the three treatments: indomethacin 25 mg q.i.d., naproxen 250 mg b.i.d., or naproxen 500 mg q.h.s. After four weeks of each of the three treatments, the third treatment was repeated for an additional four weeks to measure carry-over effect.

Results:

Indomethacin caused a statistically significant increase in grip strength as compared to b.i.d. naproxen, but no difference when compared to naproxen, 500 mg h.s. Otherwise, comparison of the three treatments revealed very similar efficacy. There was also no statistical difference in gastrointestinal ADR among the three treatments; however, indomethacin produced a greater number of CNS ADR, particularly headache and vertigo.

D. A. Calin et al. Sulindac in ankylosing spondylitis. JAMA 242:1885-6, 1979: randomized, double-masked and parallel 6-month study of 30 adult outpatients of both sexes with A.S. who received either indomethacin, 75 to 150 mg daily, or sulindac (Clinoril), 200 to 400 mg daily.

Results

No statistically significant interdrug differences were found in the following seven variates - which all improved from baseline: anterior spine flexion, right lateral flexion, left lateral flexion, chest expansion, intermalleolar straddle, muscle spasms, and finger-to-floor distance.

"The incidence of side effects was similar in both groups; no adverse reactions required discontinuance of therapy."

E. R. Sturrock et al. Double-blind cross-over comparison of indomethacin, flurbiprofen and placebo in ankylosing spondylitis. Ann Rheum Dis 33: 129-131, 1974:

24 patients were selected for inclusion in the three-way cross-over study; each patient was randomly and double-blindly assigned to one of six possible treatment sequences. Treatment with each drug (indomethacin 75 mg/day, flurbiprofen 150 mg/day, or a lactose placebo continued for two weeks. Efficacy variates included subjective patient assessment of pain, duration of morning stiffness, chest expansion and range of spinal mobility.

Results:

Indomethacin and flurbiprofen were effective and superior to placebo. Flurbiprofen was superior to indomethacin as analgesic; indomethacin was superior to flurbiprofen in increasing chest expansion. Improvement in spinal mobility was similar during both drug treatment periods, and both were statistically different from placebo.

ADR were recorded 13 times during indomethacin, 10 times during flurbiprofen, and 6 times during placebo administration. Two indomethacin, one flurbiprofen, and one placebo patient withdrew because ADR.

F. J. Wanka et al. Treatment of osteoarthritis of the hip with indomethacin. Ann Rheum Dis 23: 288-294, 1969.

Randomized, double-masked, cross-over, placebo-controlled study of twenty patients with coxarthrosis who took placebo for 4 weeks, and indomethacin for 4 weeks, beginning at 75 mg/day in week one, and progressing to 150 mg/day by week three. Efficacy variates included patient preference and range of hip motion.

Results:

14/18 patients preferred indomethacin for relief of effort pain; 12/18 preferred indomethacin for relief of rest pain; 13/18 showed definite improvement in intermalleolar distance during indomethacin therapy. Incidences of ADR were double during indomethacin treatment with one patient discontinuing it because of indigestion and giddiness. Laboratory tests were WNL.

G. B. Owen-Smith et al. Ibuprofen in the management of osteoarthritis of the hip. Rheum Phys Med 11:281-6, 1972:

Randomized, double-masked and cross-over study of 42 patients with coxarthrosis who were first given placebo for one week, then either indomethacin, 75 mg/day, or ibuprofen, 600 mg/day, or placebo, each for one week. Efficacy variates included patient assessment of pain, morning stiffness duration, intermalleolar straddle, intercondyles distance, lateral rotation of hip. 25 patients completed the study (the majority of the remaining 17 patients were not included in the analysis because of ingestion of extra analgesics during the 4-week period).

Results:

Indomethacin was superior to ibuprofen and placebo in pain relief ($p < 0.05$) improvement in intermalleolar straddle, in intercomdylar distance, and in lateral rotation (all three at $p < 0.01$). The incidence of ADR was 16% for indomethacin, 4% for ibuprofen, and none for placebo.

In a second trial, ibuprofen dosage was doubled (1200 mg/day), and indomethacin was still significantly better in relieving pain.

H. R. Hodgkinson et al. A five-year clinical trial of indomethacin in osteoarthritis of the hip. Practitioner 210: 392-6, 1973:

45 patients with coxarthrosis were given indomethacin, starting at 50 mg/day and increasing by 15 mg/day each week until the optimum dose was reached. At 3 months, 1, 2, 3, 4, and 5 years, patients were given placebo capsules for two weeks and indomethacin capsules for two weeks in a random sequence.

Results

Indomethacin was rated superior to placebo at $p < 0.01$ at 3 months, 1, 2, and 3 years, and at $p < 0.05$ at 4 and 5 years. The dose of indomethacin to control symptoms increased from a mean of 85 mg/day at 3 months to 155 mg/day by year 5. 8/45 dropped out during the first three months because of CNS or GI ADRs. 2/45 patients required operations for perforated gastric ulcers after receiving indomethacin for two years.

I. C. Smyth et al. Comparison of indomethacin and phenylbutazone in acute gout. Ann Rheum Dis 32:351-3, 1973:

28 patients with 31 acute gouty attacks received in a randomized, double-masked and parallel design either indomethacin, 50 mg q.6.h. x 24 hours, 50 mg q.6.h. for the second 24 hours, then 25 mg q.6.h. until one day after all signs of imflammation had subsided or phenylbutazone, 200 mg q.6.h. x 24 hours, etc. in the same fashion. Efficacy variates, evaluated daily, included volumes of affected and unaffected extremities, pain, tenderness, redness, heat and swelling, and patient assessments.

Results:

Reduction in volume of affected and unaffected extremities was significantly more marked ($p < 0.01$) in the indomethacin group, with the phenylbutazone groups showing an actual increase in volume of unaffected extremities (apparently due to sodium retention). Indomethacin also produced a more rapid improvement in signs and symptoms, although there were three recurrences of acute gouty arthritis in few days in the indomethacin group vs. one recurrence in the phenylbutazone group. Phenylbutazone was more effective in reducing SUA levels. No significant ADR were reported.

J. A. Ruotsi et al. Treatment of acute gouty arthritis with proquazone and indomethacin. Scand J Rheum Suppl 21: 15-17, 1978: randomized, double-masked and parallel 10-day study of 18 patients with acute gouty arthritis and elevated SUA who received initially either proquazone, 300 mg t.i.d., or indomethacin, 50 mg t.i.d. with both dosages being reduced to b.i.d. during remission. Efficacy variates included spontaneous pain, swelling, redness, pain on pressure, global evaluation by the patient and by the physician.

Results:

Indomethacin had a significant decrease in spontaneous pain and pain on pressure by day one and in swelling and redness by day two. Proquazone produced similar significant changes, although the time of improvement was slightly delayed for 3/4 symptoms. Physician global assessment revealed complete remission in 6/9 proquazone and in 4/9 indomethacin patients, which corresponds to the number of patients in each group with the diagnosis of primary gout. No ADR were reported in the indomethacin group, while 1/9 proquazone patients had GI complaints.

The following is a supportive study: N. Rothermich. An extended study of indomethacin. JAMA 195:1102-6, 1966: 2/16 patients, including 117/216 R.A., 22/216 A.S., 15/216 O.A., and 14/216 chronic gouty polyartnritis, were treated for up to 42 months with indomethacin, 100 to 200 mg daily, in an open design.

Results:

88/117 (75%) R.A. patients had good or excellent response; 44/69 patients who had been receiving corticosteroids, were able to reduce their steroid dosages by 25 to 100%.

10 2 A.S., 10/15 O.A., and 11/14 gouty arthritis patients also ienced good or excellent responses; in 72% of these p ents, the effective daily maintenance dose of indomethacin wa 100 mg or less.

The incidence of ADR during the study was not reported.

III." SAFETY

A. J. Beirne et al. Gastrointestinal blood loss caused by tolmetin, aspirin, and indomethacin. Clin Pharmacol Ther 16:821-5, 1974.

30 healthy volunteers, 15F, 15M, received the drugs for 4 days (males) or six days (females) as follows:

10/30 tolmetin, 300 mg q.i.d.,
10/30 aspirin, 975 mg q.i.d.
10/30 indomethacin, 50 mg q.i.d.

Results:

The mean daily fecal blood loss was:

0.5 ml in the control period,
1.2 ml in the tolmetin patients,
6.1 ml in the aspirin patients, and
2.1 ml in the indomethacin patients.

Conclusion:

Aspirin produced a significantly (p 0.01 by ANOVA) greater mean daily fecal blood loss (^{51}Cr) than tolmetin and indomethacin and that was significantly greater than the control blood loss ($p \ll 0.01$ by Rank test); the difference between tolmetin and indomethacin did not reach statistical significance, neither was there a statistically significant increase of the control mean daily fecal blood loss after tolmetin and indomethacin. 4/10 indomethacin-treated subjects experienced headache, 1/10 nausea, and 1/10 abdominal cramps. 5/10 aspirin-treated subjects had ADR compared to 0/10 for tolmetin.

B. P.L. Friedman et al. Coronary vasoconstrictor effect of indomethacin in patients with coronary-artery disease. NEJM 305: 1171-5, 1981.

Excerpt from summary: "Thus, despite an increase in myocardial oxygen demand, coronary blood flow fell and coronary vascular resistance increased. This coronary vasoconstrictor effect may have been due to blockade of vasodilatory prostaglandin synthesis or to a direct drug effect. Whatever the mechanism, indomethacin should be used with caution in patients with severe coronary-artery disease."

C. P.D. Mitnick et al. Effects of two nonsteroid anti-inflammatory drugs, indomethacin and oxaprozine, on the kidney. Clin Pharmacol Ther 28: 680-9, 1980.

Excerpts from summary: "Although neither drug had a long-term effect on glomerular filtration rate (GFR) or sodium clearance (C_{Na}), indomethacin (six subjects) but not oxaprozin (seven subjects) transiently reduced GRF and C_{Na}."

"Inference from clearance data...suggested that both drugs stimulated proximal tubular sodium and fluid resorption. Both suppressed aldosterone levels comparably and reduced potassium excretion transiently, but only indomethacin caused a sustained raise in serum potassium."

D. N.O. Rothermich. An extended study of indomethacin. JAMA 195: 531-6, 1966. Excerpts from summary: "The effects of indomethacin were studied in the human on long-term therapy in 234 patient-trials and on large-dose acute toxicity trials in six patients. Side effects were limited to the CNS with symptoms of headache, vertigo, light-headedness, and disturbed sensorium, and to the gastrointentinal system with symptoms of epigastric pain, cramping, and peptic ulceration. The CNS side effects were quite frequent, reaching a total incidence of 47.1% and were severe enough in 20% to require discontinuance of the drug. These side effects are of a transient nature without residuals or sequelae and disappear promptly on cessation of the drug. The gastrointentinal symptoms were less frequent, and in only 12.5% were they severe enough to warrant cessation of the drug. The high incidence of side effects was influenced by the exceptionally high doses used in this experimental study. The incidence in clinical therapy would be much lower."

N.B. "...the average daily dosage was established at 75 mg in mild cases, 125 mg in moderate, and 200 mg or more in severe."

"26 patients have been receiving indomethacin for 30 or more months."

IV. CONCLUSIONS AS TO EFFECTIVENESS - BASED ON PUBLISHED MEDICAL LITERATURE

A. RHEUMATOID ARTHRITIS

Three adequate and well-controlled studies of 180 adult patients of both sexes demonstrated clinical equivalence of indomethacin to three NSAID (phenylbutazone, aspirin, naproxen) in the treatment of active definite or classical R.A. (cf. par. III. A., B., and C. above).

B. ANKYLOSING SPONDYLITIS

Two adequate and well-controlled studies of 54 adult patients of both sexes demonstrated clinical equivalence of indomethacin to two NSAID (sulindac, flurbiproxen) in the treatment of A.S. (cf. par. III'. D. and E. above).

C. COXARTHROSIS

Two adequate and well-controlled studies of 62 patients of both sexes demonstrated superior effectiveness of indomethacin over placebo and clinical equivalence to ibuprofen, resp.; in addition, a 5-year open study with yearly 2-week single-masked placebo periods, showed superiority of indomethacin in the treatment of coxarthrosis (cf. par. III'. F., G., and H. above).

D. ACUTE GOUTY ARTHRITIS

Two adequate and well-controlled studies of 46 adult patients demonstrated slight superiority of indomethacin over phenylbutazone and its clinical comparability to proquazone in the treatment of acute gouty arthritis.

E. SUPPORTIVE STUDY: R.A., A.S., O.A., and gouty arthritis.

An open-design study of approximately 3-1/2 years duration showed continuous effectiveness of indomethacin in the treatment of 117 patients with R.A., 26 patients with A.S., 15 patients with O.A., and 15 patients with gouty arthritis.

V. CONCLUSIONS AS TO SAFETY-BASED ON PUBLISHED MEDICAL LITERATURE

A. Significantly lower fecal blood loss was found in indomethacin-treated patients than in aspirin-treated patients, and no significantly higher fecal blood loss as compared to tolmetin (cf. par. III". A. above).

B. Indomethacin causes coronary vasoconstriction in patients with coronary-artery disease (cf. par III". B. above).

C. Indomethacin transiently reduced glomerular filtration rate and renal sodium clearance rate (cf. par III". C. above).

D. In a long-study, CNS ADR required discontinuance in 20% (of 234) patients, while GI ADR required cessation of treatment in 12.5% of patients.

E. There are 60 reports of ADR and six deaths associated with each million prescriptions for indomethacin as estimated by M.F. Cuthbert. Adverse reactions to non-steroidal antirheumatic drugs. Curr Med Res Opin 2: 600-9, 1974.

F. In a study of 113 patients receiving 1.1 mg/kg/day of indomethacin, ADR were most often reported in the first 48 hours (78/113), with 28/113 complaining between 48 hours and 28 days and 7/113 complaining after 28 days of treatment. The non-gastrointestinal reactions appear early, while dyspepsia occurs after a long period of treatment. P. Boardman et al. Side-effects of indomethacin. Ann Rheum Dis 26: 127-132, 1967.

G. In 35 reports involving 2,487 patients treated with indomethacin, nausea occurred in 12%, severe abdominal pain in 3.2%, peptic ulcers in 2.1%. Wm. O'Brien. Indomethacin, a survey of clinical trials. Clin Pharm Ther 9: 94-107, 1968.

H. R. Taylor, E. Huskisson et al. Gastric ulceration occurring during indomethacin therapy. Brit Med J 4: 734-7, 1968 report of gastric ulceration occurring in 10 patients receiving indomethacin for 2 months to 2 years at the mean daily dose of 116 mg (63 to 200 mg). 3/10 had ulcers with a diameter of 4.5 to 5 cm; 6/10 had prepyloric or pyloric ulcers. In 7/10, the ulcer healed completly after withdrawal of indomethacin; of the remaining 3/10 patients, 1/3 died before withdrawal of indomethacin, 1/3 had gastrectomy, and 1/3 had a recurrent ulcer 9 months after withdrawal of indomethacin.

I. 10 patients with R.A. receiving indomethacin 150 mg daily for one week had a statistically significant increase in GI blood loss (3.4 ml/day vs. 0.8 ml/day during control period). A dose of 75 mg/day did not produce significant GI blood loss. C. Johansson et al. Gastroenterology 78: 479-483, 1980.

J. M. Thompson et al. Further experience with indomethacin in the treatment of rheumatic disorders. Brit Med J 1:80-3, 1966: 7/137 patients treated with indomethacin for rheumatic disorders experienced major neurological disturbances: 4/7 severe depression, 1/7 coma, 1/7 seizures, 1/7 hallucinations.

In this and other studies, the CNS disturbances were transient with prompt relief after discontinuane of the drug, and without residual effects. Gradual introduction of indomethacin appeared to lessen the prevalence of neurological signs and symptoms.

VI. LABELING

Identical to that for Indocin (indomethacin MSD) except for deletion of acute painful shoulder.

VII. SUMMARY OF BASIS OF APPROVAL

cf. par IV. and V. above.

VIII. RECOMMENDATION:

Approval of NDA 18-730.

Ochota 3-26-82

Leszek Ochota, M.D., Sc.D.

Drafted 2/26/82

cc: Orig NDA-18-730
HFD-150
HFD-180
HFD-150/LOchota
HFD-150/CSO/RPodliska
FT by: PCunningham/6952A

[redacted]

J S Hunter MD
for
3/26/82

N 18731

NDA 18-731

AP/LTR

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-731

SEP 29 1986

Bristol-Myers Company
Attention: Frank Furth, M.D.
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

Dear Dr. Furth:

Please refer to your new drug application dated December 18, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation BuSpar® (buspirone hydrochloride) tablets, NDA 18-731.

We also acknowledge receipt of your additional communications dated:

July 9, 1986
July 22, 1986
August 5, 1986
August 19, 1986
August 20, 1986
August 22, 1986
August 28, 1986
August 28, 1986
September 2, 1986
September 2, 1986
September 3, 1986
September 4, 1986
September 5, 1986

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that buspirone is safe and effective for use as recommended in the revised labeling that was developed at our meeting of August 29, 1986 and in subsequent telephone conversations. The application is approved effective as of the date of this letter. The Final Printed Labeling (FPL) must be identical to that incorporated in the body of this letter. Marketing the product with FPL that is not identical to that labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL (including container and package labeling) to the FDA as soon as available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA. Approval of this supplement by the FDA is not required before the labeling is used.

In addition to the submission of revised labeling, the approval of the application is conditioned upon your commitment, made earlier, to conduct a Phase IV post-marketing study to determine to what degree prior exposure to benzodiazepine treatment affects the clinical efficacy of BuSpar®.

With regard to biopharmaceutical requirements, we acknowledge your agreement to conduct 1) an appropriate Phase IV multiple dose bioavailability study comparing the 5 mg and 10 mg ovoid-rectangular (pillow-shaped) tablets and a reference oral solution, and 2) an appropriate in vitro protein binding study to determine the effect of highly protein bound drugs on the protein binding of buspirone. The Division of Biopharmaceutics has agreed to lower the dissolution specification from Q = 85% to Q = 80% in 30 minutes. Finally, the Division of Biopharmaceutics agrees with your decision to include bioavailability data for the pillow-shaped tablets rather than that of the round tablets in the labeling, provided that you agree to update the bioavailability/pharmacokinetic information in the labeling when the Phase IV steady state bioavailability study is completed.

The approved labeling of BuSpar^{R} follows:

Final Labeling:
September 15, 1986

BuSpar^{R} tablets (buspirone hydrochloride)

DESCRIPTION:

BuSpar^{R}tm (buspirone hydrochloride) is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.

BuSpar^{R} is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, BuSpar^{R} is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione monohydrochloride. The empirical formula $C_{21}H_{31}N_5O_2$ HCl is represented by the following structural formula:

[Formula].

BuSpar^{R} is supplied for oral administration in 5mg and 10mg white, ovoid-rectangular, scored tablets. BuSpar^{R} tablets, 5 mg and 10 mg, contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY:

The mechanism of action of BuSpar^{R} is unknown. BuSpar^{R} differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. *In vitro* preclinical studies have shown that buspirone has a high affinity for serotonin-1A ($5\text{-}HT_{1A}$) receptors. BuSpar^{R} has no significant affinity for benzodiazepine receptors and does not affect GABA binding *in vitro* or *in vivo* when tested in preclinical models.

BuSpar^R has moderate affinity for D_2 dopamine receptors. Some studies suggest that BuSpar^R may have indirect effects on other neurotransmitter systems.

BuSpar^R is rapidly absorbed in man and undergoes extensive first pass metabolism. In a radiolabeled study, unchanged BuSpar^R in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged BuSpar^R are very low and variable between subjects. Peak plasma levels of 1 to 6 ng/ml have been observed 40 to 90 minutes after single oral doses of 20 mg. The single dose bioavailability of unchanged BuSpar^R when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of BuSpar^R have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (Cmax) of unchanged BuSpar^R increased by 84% and 116% respectively, but the total amount of buspirone immuno-reactive material did not change. This suggests that food may decrease the extent of presystemic clearance of BuSpar^R, but the clinical significance of these findings is unknown.

A multiple dose study conducted in fifteen subjects suggests that BuSpar^R has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single dose studies.

In man, approximately 95% of BuSpar^R is plasma protein bound, but other highly bound drugs, e.g., phenytoin, propranolol and warfarin are not displaced by BuSpar^R from plasma protein in vitro. However, in vitro binding studies show that BuSpar^R does displace digoxin.

BuSpar^R is metabolized primarily by oxidation producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinyl piperazine (1-PP). In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of BuSpar^R, but is present in up to 20 fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to BuSpar^R do not exhibit high levels of 1-PP; mean values are approximately 3ng/ml and the highest human blood level recorded among 108 chronically dosed patients was 17ng/ml, less than 1/200th of 1-PP levels found in animals given large doses of BuSpar^R without signs of toxicity.

In a single dose study using ^{14}C labeled BuSpar^R, 29 to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18 to 38% of the dose. The average elimination half-life of unchanged BuSpar^R after single doses of 10 to 40 mg is about 2 to 3 hours.

The pharmacokinetics of BuSpar® in patients with hepatic or renal dysfunction have not been determined, nor has the effect of age. The effect of BuSpar® on drug metabolism or concomitant drug disposition has not been investigated.

INDICATIONS AND USAGE:

BuSpar® is indicated for the management of anxiety disorders or the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of every day life usually does not require treatment with an anxiolytic.

The efficacy of BuSpar® has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (300.02) of the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as described below:

Generalized, persistent anxiety (of at least one month continual duration), manifested by symptoms from three of the four following categories.

1. Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

2. Autonomic hyperactivity: sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, light-headedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.

4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia.

The effectiveness of BuSpar® in long term use, that is, for more than three to four weeks, has not been demonstrated in controlled trials. However, patients have been treated with BuSpar® for several months without ill effect. Therefore, the physician who elects to use BuSpar® for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS:

BuSpar^{R} is contraindicated in patients hypersensitive to buspirone hydrochloride.

WARNINGS:

Because BuSpar^{R} has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:

General:

Interference with Cognitive and Motor Performance:

Studies indicate that BuSpar^{R} is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar^{R} with alcohol indicate that buspirone does not increase alcohol induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug Dependent Patients:

Because BuSpar^{R} does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar^{R}, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and, occasionally, even as seizures.

Possible Concerns Related to Buspirone's Binding to Dopamine Receptors:

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:

To assure safe and effective use of BuSpar^{R}, the following information and instructions should be given to patients:

1. Inform your physician about any medications, prescription or non-prescription, alcohol or drugs that you are now taking or plan to take during your treatment with BuSpar^{R}.

2. Inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking BuSpar^{R}.

3. Inform your physician if you are breast feeding an infant.

4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.

Laboratory Tests:

There are no specific laboratory tests recommended.

Drug Interactions:

Because the effects of concomitant administration of BuSpar^{R} with most other psychotropic drugs have not been studied, the concomitant use of BuSpar^{R} with other CNS active drugs should be approached with caution.

There is one report suggesting that the concomitant use of Desyrel (trazodone) and Buspar may have caused 3 to 6 fold elevations in SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

BuSpar^{R} does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins. However, it may displace less firmly bound drugs like digoxin; the clinical significance of this property is unknown.

Drug/Laboratory Interactions:

BuSpar^R is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No evidence of carcinogenic potential was observed in rats during a 24-month study at approximately 133 times the maximum recommended human oral dose; or in mice, during an 18-month study at approximately 167 times the maximum recommended human oral dose.

With or without metabolic activation, BuSpar^R did not induce point mutations in 5 strains of Salmonella typhimurium (Ames Test) or mouse lymphoma L5178YTK$^+$ cell cultures, nor was DNA damage observed with BuSpar^R in Wi-38 human cells. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given one or five daily doses of BuSpar^R.

Pregnancy:Teratogenic Effects:

Pregnancy Category B: No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at BuSpar^R doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well controlled studies during pregnancy have not been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

The effect of BuSpar^R on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

Nursing Mothers:

The extent of the excretion in human milk of BuSpar^R or its metabolites is not known. In rats, however, BuSpar^R and its metabolites are excreted in milk. BuSpar^R administration to nursing women should be avoided if clinically possible.

Pediatric Use:

The safety and effectiveness of BuSpar^R has not been determined in individuals below 18 years of age.

Use in the Elderly:

BuSpar^R has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with BuSpar^R, and no unusual adverse age related phenomena have been identified. In 87 elderly patients for whom dosage data were available, the modal total daily dose of BuSpar^R was 15 mg/day, the same as that in the total sample of patients treated with BuSpar^R.

Use in Patients with Impaired Hepatic or Renal Function:

Since BuSpar® is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also PRECAUTIONS):

Commonly Observed:

The more commonly observed untoward events associated with the use of BuSpar® not seen at an equivalent incidence among placebo treated patients include dizziness, nausea, headache, nervousness, lightheadedness, excitement.

Associated with Discontinuation of Treatment:

One guide to the relative clinical importance of adverse events associated with BuSpar® is provided by the frequency with which they caused drug discontinuation during clinical testing. Approximately ten percent of the 2200 anxious patients who participated in BuSpar®'s premarketing controlled clinical trials, lasting three to four weeks, discontinued treatment due to an adverse event.

The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness and lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:

The table that follows enumerates adverse events that occurred at a frequency of 1% or more among BuSpar® patients who participated in four week, controlled trials comparing BuSpar® with placebo. The frequencies were obtained from pooled data for seventeen trials. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. Comparison of the cited figures, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Treatment Emergent Adverse Experience Incidence
in Placebo-Controlled Clinical Trials*
(Percent of Patients Reporting)

Adverse Experience	BuSpar® (n=477)	Placebo (n=464)
Cardiovascular		
Tachycardia/Palpitations	1	1
CNS		
Dizziness	12	3
Drowsiness	10	9
Nervousness	5	1
Insomnia	3	3
Lightheadedness	3	-
Decreased Concentration	2	2
Excitement	2	-
Anger/Hostility	2	-
Confusion	2	-
Depression	2	2
EENT		
Blurred Vision	2	-
Gastrointestinal		
Nausea	8	5
Dry Mouth	3	4
Abdominal/Gastric Distress	2	2
Diarrhea	2	-
Constipation	1	2
Vomiting	1	2
Musculoskeletal		
Musculoskeletal Aches/Pains	1	-
Neurological		
Numbness	2	-
Paresthesia	1	-
Incoordination	1	-
Tremor	1	-
Skin		
Skin Rash	1	-
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	-
Sweating/Clamminess	1	-

(*) Events reported by at least 1% of Buspar patients are included.
(-) Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of Buspar:

During its premarketing assessment, Buspar was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of BuSpar^{R} in the dose range for which BuSpar^{R} is recommended (i.e., the modal daily dose of BuSpar^{R} fell between 10 and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to Buspar varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to BuSpar^{R} treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the PRECAUTIONS section.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia.

Central Nervous System: Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, slurred speech and psychosis.

EENT: Frequent were tinnitus, sore throat, and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear "abnormality", eye pain, photophobia, and pressure on eyes.

Endocrine: Rare were galactorrhea and thyroid abnormality.

Gastrointestinal: Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue.

Genitourinary: Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia.

Musculoskeletal: Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias.

Neurological: Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness.

Respiratory: Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis.

Sexual Function: Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.

Skin: Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne, and thinning of nails.

Clinical Laboratory: Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia.

Miscellaneous: Infrequent were, weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alchohol abuse, bleeding disturbance, loss of voice and hiccoughs.

NON-DOMESTIC POST-MARKETING EXPERIENCE:

Foreign post-marketing experience has shown an adverse experience profile similar to that given above and no other unexpected adverse reactions have been reported to date.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Class:

BuSpar^{R} is not a controlled substance.

Physical and Psychological Dependence:

In human and animal studies, BuSpar^{R} has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. Human volunteers with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between BuSpar^{R} and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that BuSpar^{R} lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of BuSpar^{R} did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that BuSpar^R causes physical dependence or drug seeking behavior, it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BuSpar^R misuse or abuse (e.g., development of tolerance, incrementation of dose, drug seeking behavior).

OVERDOSAGE:

Signs and Symptoms:

In clinical pharmacology trials, doses as high as 375 mg a day were administered to healthy male volunteers. As this dose was approached, the following signs were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage of BuSpar^R. Toxicology studies of BuSpar^R yielded the following LD_{50} values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160-550 times the recommended human daily dose.

Recommended Overdose Treatment:

General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to BuSpar^R, and dialyzability of BuSpar^R has not been determined.

DOSAGE AND ADMINISTRATION:

The recommended initial dose is 15 mg daily (5 mg three times a day). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20-30mg per day were commonly employed.

HOW SUPPLIED:

BuSpar^R (buspirone hydrochloride)

Tablets, 5 mg and 10 mg (white, ovoid-rectangular with score, MJ logo, strength and the name BuSpar^R embossed) are available in bottles of 100.

NDC 0087-0818-41 5 mg tablet	Bottles of 100
NDC 0087-0819-41 10 mg tablet	Bottles of 100

Store at Room Temperature - Protect from Temperatures greater than 86°F (30°C).

REFERENCE
1. Williams, JWB, Ed.: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association, May 1980.

END OF TEXT

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of the labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

AE/LTR

HFN-120

JUL 17 1986

NDA 13-731

Bristol-Myers Company
Attention: Frank Furth, M.D.
Regulatory Affairs
Wallingford, Connecticut 06492-7660

Dear Dr. Furth:

Please refer to your New Drug Application dated December 15, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation BUSPAR (buspirone hydrochloride) tablets.

Please also refer to your submissions dated

January 19, 1983	January 18, 1984	December 4, 1985
February 4, 1983	January 19, 1984	December 9, 1985
March 10, 1983	February 17, 1984	December 16, 1985
March 31, 1983	March 21, 1984	January 20, 1986
April 28, 1983	April 11, 1984	February 3, 1986
May 10, 1983	July 5, 1984	February 26, 1986
May 16, 1983	July 6, 1984	March 3, 1986
May 16, 1983	July 6, 1984	March 11, 1986
June 13, 1983	July 19, 1984	March 13, 1986
August 22, 1983	August 9, 1984	March 17, 1986
September 29, 1983	September 6, 1984	March 17, 1986
October 3, 1983	September 27, 1984	March 26, 1986
October 6, 1983	December 21, 1984	March 26, 1986
October 26, 1983	January 11, 1985	April 1, 1986
November 11, 1983	July 29, 1985	April 1, 1986
November 21, 1983	August 19, 1985	June 17, 1986
December 2, 1983	October 10, 1985	June 19, 1986
December 2, 1983	November 13, 1985	June 25, 1986
December 16, 1983	December 3, 1985	

We have completed our review of the application as submitted with draft labeling. We find the application approvable for the use of buspirone in the management of anxiety disorders and the short term relief of the symptoms of anxiety. We do not find the data and evidence provided sufficient, however, to justify a qualification of the claimed indication regarding the efficacy of the product in the presence of depressive symptomatology exhibited by primarily anxious patients. Depressive symptoms are common in primary anxiety disorders and would not be expected to influence the anxiolytic efficacy of an anxiolytic drug. To support specific language related to use in depression you would need to evaluate the anxiolytic efficacy of buspirone in primarily depressed patients.

Final approval of the application will require 1) a brief summary of any new information accumulated in the interval between December 1, 1985 (the completion of your major safety update) and the date of your receipt of this letter that bears on the safety of buspirone, 2) revision of your proposed labeling as indicated, 3) your agreement to the conditions described in the section of this letter entitled "Biopharmaceutic Requirements," and 4) your commitment to conduct a post marketing study to be initiated within the first year of marketing, that will prospectively explore the apparent differential responsiveness to Buspar among anxious patients with and without prior benzodiazepine treatment.

1) Brief Interim Safety Summary:

This report is intended to provide the agency with any new information that might affect a decision on the approvability and/or labeling of buspirone.

2) Labeling:

Accompanying this letter (Attachment 1) is the agency's proposal for the labeling of BUSPAR. We believe it presents a fair summary of the information available on the benefits and risks of Buspar and that, in part because the labeling was developed in the course of joint negotiations between your staff and ours, you will have no major disagreement with its format and content. If you disagree with specific points, we would of course be happy to discuss them.

Please provide several copies of proposed final labeling in final printed format. This presentation of labeling will facilitate our final review. In addition, please submit in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacology, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not for proposed materials.

3) Biopharmaceutic Requirements:

A) The application for the 5mg, 10mg round and pillow shaped tablets is approvable provided you agree to carry out the following phase IV studies expeditiously and submit the results to the Agency for evaluation:

1) A multiple dose bioavailability study comparing the 5mg, 10mg, round tablets and a reference solution in which both unchanged buspirone and 1-PP plasma levels are determined. A multiple dose study is needed because buspirone appears to exhibit nonlinear pharmacokinetics and results obtained in a single dose study may not be predictive of the steady state. Measurement of both unchanged buspirone and 1-PP is needed because unchanged buspirone concentrations in plasma following oral administration are very low and variable, and 1-PP, a major metabolite of buspirone, is pharmacologically active and may contribute significantly to the therapeutic effect of buspirone. This study should be conducted as soon as a suitable assay for 1-PP becomes available.

11) An in vitro protein binding study to determine the effect of highly protein bound drugs on the protein binding of buspirone (if such a study has not been conducted). This study is needed because buspirone is highly protein bound (95%).

B) Regarding the dissolution methodology and specification of this NDA 18-731:

1) You have developed a rotating paddle method which is listed below:

USP Apparatus II (paddle)
500 ml 0.01N HCl at 37°C
50 rpm

This proposed method is acceptable.

2) You have proposed the following Dissolution Specification:

NLT 85% dissolved in 30 min.

The proposed Specification is acceptable.

C) Please forward 300 units of each tablet strength to Dr. V.K. Prasad, Chief of Biopharmaceutics Research Branch, HFN-224, FOB-8,Rm 6067, 200 C Street S.W., Washington, D.C. 20204.

D) Our approval does not apply to reprocessed drug product. However, should you desire to market reprocessed drug, it may be possible to do so if you can satisfy the usual bioavailability/bioequivalence requirements.

This concludes our comments regarding the biopharmaceutics requirements.

4) Clinical Requirements:

We acknowledge your recent submissions (June 17 and 19, 1986) of additional analyses of efficacy data from the Rickels, Bohn and Peckhold studies, based on the stratification of patients regarding prior benzodiazepine use. These data suggest that prior benzodiazepine exposure might influence responsiveness to buspirone treatment, i.e., patients without prior benzodiazepine treatment appear to respond more positively to buspirone treatment than patients with prior benzodiazepine treatment. This is a potentially important finding and needs further study in order to obtain reliable prospective data that could serve as a basis for labeling that would provide adequate directions for the use of Buspar. Therefore, we ask that you agree to conduct a phase IV study to further explore this apparent differential responsiveness. You are encouraged to consult with Division of Neuropharmacological Drug Products staff in designing a post marketing study of this finding.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action the FDA may take action to withdraw the application.

This drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-3830.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig:NDA
HFN-120
HFN-226/Dr.Yau
HFN-120/FZinsitz/RShultz
HFN-120/JContrera
HFN-120/KKook/TLaughren/PLeber
HFN-120/TDeCicco
DRAFT by LEBER/LAUGHREN
ad/7/3/86
ft/pjd/7/8/86:7/11/86
DOC 2938C

SBA

NDA 18-731

Summary Basis of Approval

NDA 18-731

Drug Generic Name:
Buspirone Hydrochloride

Applicant:
Bristol Myers Company
Evansville, Indiana

Drug Trade Name:
BUSPAR®

I. Indications for Use:

BUSPAR is indicated for the management of anxiety disorders or the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of every day life usually does not require treatment with an anxiolytic.

The efficacy of BUSPAR has been demonstrated in controlled clinical trials of outpatients whose diagnosis would correspond to Generalized Anxiety Disorder (300.02) of the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as described below:

Generalized, persistent anxiety (of at least one month continual duration), manifested by symptoms from three of the four following categories.

1. Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

2. Autonomic hyperactivity: sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, light-headedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.

4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge," irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia.

[1]Williams, JWB, Ed.: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association, May 1980.

The effectiveness of BUSPAR in long term use, that is, for more than four weeks, has not been demonstrated in controlled trials. Therefore, the physician who elects to use BUSPAR for extended periods should periodically reassess the usefulness of the drug for the individual patient.

II. Dosage Form, Route of Administration and Recommended Dosage:

Buspar is available as 5 and 10 mg ovoid-rectangular (pillow-shaped) tablets, with the name Buspar raised on one surface and a score and HU with the number 5 or 10 engraved on the opposite side, and is for oral use.

The recommended initial dose is 15 mg daily (5 mg three times a day). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20-30 mg per day were commonly employed.

III. Manufacturing and Controls:

A. Manufacturing and Controls:

The description of the multiple step synthesis of buspirone hydrochloride is supported with experimental data to establish the identity, strength, quality, and purity of the new drug substance.

Specifications and tests for the new drug substance are in agreement with the data used for the characterization of the reference standard.

The manufacturing and control procedures for the tablets are adequately described and supported with data obtained to demonstrate the identity, strength, quality, and purity.

B. Stability Studies:

Adequate stability data have been submitted to support the expiration dating of the drug dosage strengths packaged in high density polyethylene containers fitted with child resistant closures.

C. Methods Validation:

The analytical methods were validated by two FDA Laboratories and found satisfactory for regulatory purposes.

D. Labeling:

Draft labeling and final printed container labels include the required statements with regard to chemistry to satisfy 21CFR.

E. Establishment Inspection:

Evaluation of the facilities used for the manufacture of the drug substance and drug product as well as those used for the packaging and controls by the Office of Compliance indicate compliance with GMP's.

F. Environmental Impact Analysis Report:

A report has been provided in accordance with CFR 25(g) which is acceptable and further analysis is not necessary.

IV. Pharmacology:

Buspirone is a novel anxiolytic that is pharmacologically and structurally distinct from the benzodiazepines. While it has a behavioral profile in preclinical tests that may be predictive of anxiolytic activity, it has neither the anticonvulsant nor the muscle relaxant properties possessed by currently marketed anxiolytics. Buspirone also lacks prominent sedative-hypnotic activity within the anxiolytic dose range (1 to 5 mg/kg, p.o.).

Buspirone is also active in behavioral tests predictive of antipsychotic or neuroleptic activity, due to weak dopamine (DA)-antagonist properties, but the doses required for this activity are generally larger or must be administered parenterally. In addition, the interaction with DA receptors is quite complex and not yet fully understood or characterized. Under different conditions buspirone may resemble either a DA antagonist or an agonist. These paradoxical effects appear to be somewhat state dependent, e.g. buspirone can antagonize both the stereotypy induced by apomorphine and the catalepsy induced by neuroleptics.

The mechanism of buspirone's anxiolytic activity is as yet undetermined. In contrast to marketed anxiolytics, it has no significant affinity for benzodiazepine receptors and does not affect the binding of GABA in vitro or in vivo. The sponsor has at different times suggested the involvement of DA or 5-HT neuronal systems, but the data are insufficient to propose a primary role for either. There is evidence, however, that a significant portion of the anticonflict activity of buspirone may be due to a metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP), while the effects on DA receptor systems appear to be solely due to the parent compound.

Metabolism of buspirone is essentially complete in all species, as little or no unchanged drug could be found in urine or feces. Elimination occurs by both urinary and biliary excretion, accounting for approximately 40 to 60% and 30 to 40% of the administered dose, respectively.

In acute toxicity studies, death was preceded by clonic convulsions and profuse salivation in all species tested. Females appeared to be somewhat more sensitive than males.

Dose-related decreases in weight were seen in chronically treated rats(2 years, at doses up to 160 mg/kg/day) and mice(18 months, at doses up to 200 mg/kg/day). Other signs of toxicity in rats included rapid respiration, tremors and tachycardia. Histopathology revealed dose-related changes in the lung, termed pulmonary histiocytosis, which consisted of an accumulation of numerous enlarged alveolar macrophages in the alveolar lumens; this toxicity did not appear to adversely affect longevity.

In the 18 month mouse study, there was also weight loss due to treatment, though it was not as clearly dose-related as the weight loss in rats. Mortality was not affected by treatment. Other treatment-related effects were associated with an increased incidence of amyloid deposition in some tissues of the high dose groups. While this type of degenerative disease is a spontaneous occurrence in mice, and occurred in all 4 groups, the incidence was greater in the high dose animals, especially males. Most histological changes were related to the amyloidosis and was most apparent in renal, gastrointestinal and testicular tissues in males and ovarian tissues in females. These changes in the reproductive organs resulted in ovarian activity and testicular atrophy.

In the one year study in the monkey, neurotoxicity was evidenced within the first few months and subsequently, by behaviors such as tremor, salivation, hypoactivity and anorexia, which could be seen at the lowest dose (25mg/kg) and intensified with increasing doses between 50 and 100 mg/kg. Catatonia and repetitive chewing on the wrists and cage were also seen at higher doses, as were sedation and bloody diarrhea. In the one year study, the survivors for the control, low, mid and high dose were 4/4, 3/4, 4/5, and 3/7 for males, and 4/4, 4/4, 4/4, and 2/5 for females,respectively. The monkeys that died showed marked weight losses, while the survivors had weights similar to controls. Lab chemistry changes included decreased hemoglobin and hemocrit at mid and high dose levels and increased serum GOT and GPT in the high dose group. Organ weight changes occurred for several organs and were generally dose related, including increases in liver and adrenal weight and decreases in testes weight, although no consistent histopathological changes were noted for these organs. Areas of inflammation were found in the gastrointestinal tract.

In two carcinogenicity studies (2 year rat and 18 month mouse), no differences in the type or frequency of adenomas or carcinomas were seen. Thus, buspirone was not considered to be carcinogenic in these studies.

No evidence of mutagenicity was found for buspirone, with or without metabolic activation in 5 Ames test strains, the mouse lymphoma mutagenicity assay, the unscheduled DNA synthesis test or the in vivo cytogenetics test in mice. Reproduction studies in rats and rabbits failed to reveal any fetotoxicity or teratogenicity.

V. Clinical Evidence:

This section provides 1) a brief overview, 2) a description of the adequate and well controlled trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled trials which were either less supportive or failed to support the efficacy claim, and 4) a section on the safety findings for buspirone.

A. General:

Buspirone represents a new chemical class of anxiolytic drug products. Although originally intended as an antipsychotic agent, buspirone in doses up to 2400 mg produced only transient antipsychotic activity. Since preclinical studies also suggested a potential for anxiolytic activity, the primary focus of the clinical program for buspirone was changed to studies in patients with generalized anxiety disorder.

The results from 16 controlled trials of the safety and anxiolytic efficacy of buspirone were submitted in this NDA in support of the claim for anxiolytic efficacy. Nine of these trials were comparisons of buspirone with an active anxiolytic drug and with placebo. Seven of these trials compared buspirone with only an active control substance. Because active control studies cannot generally provide clear evidence of effectiveness, the three-way studies provide the most pertinent data on effectiveness. Among the placebo controlled trials, only 994 (Rickels) and 2044 (Bohm) provide clear evidence of effectiveness. Two other studies, [illegible]h by Goldberg, also were favorable as reported, but for reasons giv n below cannot be relied upon. Although the activ control studies do not provide evidence of effectiveness, their results are not inconsistent with the results of the two positive three way studies, i.e., they demonstrate no difference between the two active drugs studied.

B. Double Blind Studies With a Placebo Control:

The nine three-way studies include the six domestic studies [764 (Goldberg), 995 (Goldberg), 994 (Rickels), 996 (Feighner), 1012 (Smith), 1610, (Cohn)] and three foreign studies [1002 (Pecknold), 2044 (Bohm), 532 (Tyrer)]. However, the finding by the Division of Scientific Investigations (DSI) of protocol violations, previously unidentified and unmonitored co-investigators, and discrepancies between case report forms and patients' medical records for Goldberg's studies (764 and 995) resulted in a conclusion that data from these studies could not be relied upon. In addition, a DSI discovery that one of the investigators in the Rickel's study (Katz) was previously not identified and not monitored led to the decision to reanalyze this data set excluding the Katz data. Finally, one of [illegible]e foreign studies [532 (Tyrer)], a crossover study which failed to use a washout period before starting or between treatments, will not be further considered because of the serious design weaknesses. Therefore, this summary will focus on the four domestic and two foreign studies which were adequately designed and conducted.

1. Study 994: [K. Rickels is listed as the principal investigator. However, the patients were actually seen by 15 associate investigators who contributed patients from their general medical practices in Philadelphia, PA. As noted above, the data from the sixteenth investigator (Dr. Katz) were excluded.]

Design:

This was planned as a four week, double blind, parallel group comparison of buspirone, diazepam, and placebo in anxious outpatients. Patients were required to meet DSM II criteria for anxiety neurosis and to have at baseline a Hamilton Anxiety Rating Scale (HAM-A) score greater than 18, a Covi Anxiety Scale score greater than 9, and a Raskin Depression Scale score less than the Covi Anxiety Scale score. Exclusion criteria generally included: significant physical illness; significant other psychiatric disorder; neuroleptic or antidepressant use within two weeks of entry or the use of other CNS drugs within 7 days of entry.

Patients were to be randomly assigned to buspirone, diazepam, or placebo. After a one week washout, patients were then to be titrated to up to 50 mg/day of either buspirone or diazepam, or up to 10 capsules of placebo per day, on a b.i.d. schedule. The treatment period was to be four weeks. Efficacy assessments (to be done at baseline and weekly) included: HAM-A, Physician's Questionnaire, SCL-56, POMS. Periodic safety assessments (done at baseline and weekly) included: physical exam, vital signs, clinical labs, ECGs and ADRs. Concomitant psychotropic medications were prohibited.

Conduct and Execution:

Two hundred and forty subjects were entered. On reanalysis, all of these patients met DSM III diagnostic criteria for generalized anxiety disorder. However, 34 patients (from the Katz Center) were excluded from the analyses. In addition, the second participation of three patients who were re-entered were also excluded, resulting in a patient sample of 203: buspirone-69, diazepam-67, placebo-67. These patients were comparable at baseline regarding age, HAM-A total score, and duration of anxiety symptoms. Overall, 89% of these patients had anxiety symptoms for greater than three months at the time of entry. The mean buspirone dose over the four week treatment program was 23.0 mg and the mean diazepam dose was 21.0 mg.

Eighty patients dropped out before completion (buspirone-25, diazepam-21, placebo-34). The primary reason for discontinuation of placebo patients was lack of efficacy, while active drug patients who discontinued were more evenly distributed among: lack of efficacy, untoward events and miscellaneous. All treatment groups had over 80% participation at week 3, but this dropped to 52% for the placebo group and approximately 65% for both active drug groups at week 4.

Results:

In addition to excluding patients from the Katz Center and the three patients entered twice, ten patients were excluded from the analyses because of a lack of efficacy data after baseline and six additional patients were excluded because of the use of concomitant medications (buspirone-1, diazepam-5), yielding a sample of 187 patients for the efficacy analysis: buspirone-64, diazepam-59, placebo-64. The following table provides results of an analysis of covariance for HAM-A total scores, with the last observation carried forward (LOCF), at weeks 3 and 4:

Study 994 (Rickels)

Sponsor's Revised Analysis of Covariance Results
HAM-A-Total
Intent-to-Treat with Last Value Carried Forward

Response Variable	Week	Buspirone		Diazepam		Placebo		P-value(2 sided)
		n	mean	n	mean	n	mean	B vs P
Baseline	0	64	24.5	59	25.2	64	24.0	.63
Adjusted Change from Baseline	3	64	-9.4	58	-11.1	64	-3.0	.001
	4	64	-9.9	59	-12.3	64	-3.7	.001

Analyses (LOCF) for the two key items from the HAM-A (anxious mood and tension) and all measures from the Physician's Questionnaire (global psychopathology rating, as well as both physician and patient opinion of improvement) favored buspirone over placebo at both weeks 3 and 4 (p less than 0.001 for all comparisons, two sided).

Post hoc analyses were done by the sponsor based on a stratification of patients into those who did and those who did not have prior exposure to benzodiazepines. These analyses, while primarily of value in generating hypotheses for future testing, generally suggested that buspirone treated patients without prior benzodiazepine exposure were more dramatically improved relative to placebo than the buspirone treated patients with prior benzodiazepine exposure (even though both subgroups demonstrated statistically significant superiority to the respective placebo subgroups on most measures). There was less of a difference in outcome for diazepam treated patients stratified on the basis of prior benzodiazepine exposure, although here the greater effect numerically seemed to slightly favor patients with prior benzodiazepine exposure.

2. Study 2044: (The only investigator for this study was Bohm, an internist in West Germany).

Design:

This was planned as a three week, double blind, parallel group comparison of buspirone, clobazam, and placebo in anxious outpatients. These patients were required to have primary symptoms of anxiety (as evidenced by feeling nervous, jittery, jumpy). In addition, they were to have at least three symptoms from the following list:

Subjective Symptoms:
1. Fears of fainting, screaming, losing control, crowds, places, disaster, death.
2. Avoiding certain places, things or activities because of fear.
3. Feeling tense or keyed up.
4. Feeling fearful, apprehensive and panicky.

Muscular or Motor Phenomena:
5. Tense, aching muscles.
6. Trembling, shaking.
7. Restlessness, fidgeting.

Autonomic Phenomena:
8. Heart beating fast or pounding, chest pain.
9. Trouble catching breath, air hunger, smothering, lump in throat, choking.
10. Sweating, especially armpits, palms, feet.
11. Cold, clammy hands.
12. Dry mouth.
13. Dizziness, fainting, lightheadedness, weakness.
14. Tingling feeling in hands and feet.
15. Stomach "gas", nausea, upset stomach.
16. Frequency or urgency of bladder or bowels.

Symptoms were to have been present at least one month, and subjects were required to have HAM-A total scores at baseline of greater than 12. Patients were also required to be free of psychotropic drug use for seven days prior to the administration of study drug.

The plan was to randomly assign patients to buspirone, clobazam or placebo. All patients were to have a one week placebo washout, and were then to be given study drug on a b.i.d. schedule. Doses for both active drugs were 20 mg/day during week one, with increases up to a maximum of 30 mg/day during weeks two and three. Efficacy assessments (obtained at baseline and weekly) included: HAM-A and Physicians Questionnaire. There were no systematic safety assessments other than history and physical exams at baseline. The use of concomitant psychotropic medications was discouraged.

Conduct and Execution:

Sixty patients entered this trial (20 in each group). Subjects were comparable at baseline on age, sex distribution, HAM-A total score and duration of anxiety symptoms. However, not all subjects met the entry requirement that anxiety symptoms be present greater than one month:

Duration of Anxiety Symptoms	buspirone (n=20)	Clobazam (n=20)	Placebo (n=20)
2-3 weeks	2	0	1
3-4 weeks	6	7	3
1-3 months	12	13	16

P=0.37, Fishers Exact Test

Nevertheless, all but three subjects (buspirone-2, placebo-1) had symptoms for more than 3 weeks prior to entry.

The mean buspirone dose over the 3 week treatment period was 23.0 mg, while the mean clobazam dose was 21.0 mg.

Only one patient dropped out, a clobazam patient who left during the second week due to an automobile accident.

Results:

The following table provides the results of an analysis of covariance for the HAM-A total scores (LOCF) at week 3:

Study 2044 (Bohm)

Sponsor's Analysis of Covariance Results
HAM-A Total - Week 3
Intent-to-Treat with Last Value Carried Forward+

Response Variable	Buspirone n	Buspirone mean	Clobazam n	Clobazam mean	Placebo n	Placebo mean	p-value (2 sided) B vs P
Baseline	20	28.0	20	29.3	20	28.4	.79
Adjusted Change from Baseline	20	-16.1	20	-20.1	20	-4.0	.001

+Only 1 patient (on clobazam) dropped out before Week 3

Analyses (LOCF) for the two key items on the HAM-A (anxious mood and tension) and all measures from the Physician's Questionnaire (global psychopathology rating, as well as both physician and patient opinion of improvement) favored buspirone over placebo at week 3 (p less than 0.001 for all comparisons, two sided). An additional analysis omitting the buspirone and placebo patients who had symptoms less than 4 weeks at entry also favored buspirone over placebo (p less than 0.001, two sided).

Post hoc analyses of patients stratified on the basis of prior benzodiazepine exposure were also submitted. As in study 994 (Rickels), these analyses suggested that patients without prior benzodiazepine treatment were more responsive to buspirone than patients with prior benzodiazepine treatment (even though, again, both subgroups were generally statistically superior to the respective placebo subgroups). Patients with prior benzodiazepine exposure tended to be more responsive to clobazam than those without prior benzodiazepine treatment, although again, both subgroups were statistically superior to placebo.

The remaining four studies were either less supportive or unsupportive for buspirone, and will be more briefly summarized.

These four studies included: 996 (Feighner), 1012 (Smith), 1802 (Pecknold), 1610 (Cohn). All four studies involved a four week, double blind parallel group comparison of buspirone, diazepam and placebo in anxious outpatients who met DSM III criteria for generalized anxiety disorder. The following table provides for each study the number of subjects entered per group, the mean HAM-A total scores at entry and the mean doses of active drug during the trial:

Study (Investigator)	Drug	Subjects Entered	Mean Ham-A Total Score At Baseline	Mean Dose During Trial (mg/day)
996 (Feighner)	B	40	26.5	22.0
	D	40	25.6	22.5
	P	40	24.8	----
1012 (Smith	B	40	26.8	27.0
	D	40	29.2	22.0
	P	40	27.6	----
1802 (Pecknold)	B	22	25.6	19.5
	D	21	26.9	14.0
	P	20	25.8	----
1610(Cohn)	B	30	23.8	35.5
	D	30	23.3	25.0
	P	30	24.5	----

The major efficacy assessments for all four studies included: HAM-A, Physicians Questionnaire and SCL-56. All efficacy data were analyzed by analysis of covariance (LOCF).

3. Study 996 (Feighner):

The efficacy analysis was done on an evaluable subset of entered patients: B-29; D-32; P-29. Although there were scattered positive findings for diazepam over placebo, in general, these analyses did not favor either active drug over placebo.

4. Study 1012 (Smith):

The efficacy analyses were done on an evaluable subset of patients including all but three of the entered patients. The analyses did not favor buspirone over placebo on any of the efficacy measures. The outcome was generally more positive for diazepam, which was superior to placebo on several critical efficacy variables, including the HAM-A total score at weeks 3 and 4, the HAM-A anxious mood item at week 3 and the HAM-A tension item at week 4.

5. Study 1802 (Pecknold):

The efficacy analyses included all but three of the entered patients. Although the analyses favored buspirone over placebo on the HAM-A total score at week 4, there were no differences between buspirone and placebo on other critical anxiety measures. On the other hand, diazepam was superior to placebo on a majority of the anxiety measures.

Post hoc analyses of patients stratified on the basis of prior benzodiazepine exposure were also submitted for this study. As in both the Rickels (994) and Bohm (2044) post hoc analyses, there was a suggestion that patients without prior benzodiazepine exposure had a better response on buspirone treatment than those with prior benzodiazepine treatment. For some of the critical variables these subgroup analyses did not demonstrate statistical superiority for either subgroup over placebo, but buspirone treated patients without prior benzodiazepine treatment were at least numerically superior to placebo in most cases and fared better than buspirone treated patients with prior benzodiazepine exposure for almost all critical variables. The influence of prior benzodiazepine exposure on response to diazepam was less clear from these analyses.

6. Study 1610 (Cohn):

Of the ninety patients entered into the study, 89% had anxiety symptoms at least 6 months, and most, in fact, had symptoms for greater than 1 year. Ninety-six percent of these patients had prior treatment with psychotropic drugs (not specified).

The efficacy analyses were done on an evaluable subset of entered patients: B-30; D-30; P-24. Buspirone was not superior to placebo for any of the anxiety measures. The outcome was equivocal for diazepam, with diazepam being favored over placebo for the HAM-A total score only at week 4, and was no different from placebo for the anxious mood and tension items at both weeks 3 and 4. The outcome was also equivocal for diazepam on the Physician's Questionnaire.

Summary of Efficacy Data

Of the six studies considered to be adequately designed and conducted, two (Rickels and Bohm) provided strong evidence for the anxiolytic effectiveness of buspirone. Two other studies (Feighner and Cohn) were unable to demonstrate superiority of either buspirone or diazepam over placebo, and must be considered failed (null) studies, i.e., not having the ability to distinguish known active therapy such as diazepam from placebo. One of the remaining two studies (Pecknold) provided some support for buspirone although it more clearly favored diazepam; the last study, by Smith, was generally positive for diazepam and negative for buspirone.

The sponsor's post hoc analyses for the Rickels, Bohm and Pecknold studies of patients stratified on the basis of prior benzodiazepine treatment provide a possible explanation for the relatively negative outcome for buspirone in the Pecknold study. These analyses suggested that an absence of prior benzodiazepine treatment was associated with an increased likelihood of positive response to buspirone. This trend was clear in all three studies for which data were submitted. This type of post hoc analysis was less useful in the remaining three studies, as these studies tended to enroll more chronic patients, a majority of whom had prior benzodiazepine exposure, and two of them could not distinguish either active agent. While the Smith study was a sensitive assay for demonstrating the effectiveness of diazepam, it may not have had sufficient sensitivity for testing buspirone's effect, due to the population entered.

Two of the four studies that had sensitivity to test anxiolytic efficacy thus demonstrated clear superiority of buspirone over placebo. The remaining two studies were, overall, not supportive of buspirone, although the Pecknold study was weakly favorable. Differential responsiveness to buspirone depending on prior benzodiazepine exposure might provide a partial explanation for this negative outcome in these two studies. In any case, the Rickels and Bohm studies are quite strong, and provide substantial evidence for the anxiolytic efficacy of buspirone.

C. Safety:

The safety data base for buspirone includes 3558 patients who were exposed to this drug during its clinical development. In addition, safety data are provided from the post marketing experience with buspirone in West Germany.

While most of the anxious patients treated with buspirone were treated for less than three months, the data base includes 337 patients who were treated for greater than six months. While 60% of patients were treated in the range of 10-20 mg/day, the dose range for anxious patients was 5-60 mg/day.

This summary of the safety experience with buspirone will focus initially on the 3558 patients exposed to buspirone in the development program. It will begin with a discussion of patients experiencing major clinical events during buspirone treatment, then review changes in clinical laboratory values, ECGs and vital signs. A separate section will discuss patients discontinued from treatment. Data from 17 placebo controlled studies will be presented to compare ADR incidence rates for buspirone and placebo (for primary terms occurring at a frequency of greater than 1% in the buspirone patients). In addition, overall rates (for the entire population included in the computer data base) will be presented for the less frequent ADRs. The safety experience during the long-term use of buspirone will also be summarized. Finally, a summary report on prolactin elevation associated with buspirone use will be provided.

A separate section of this summary will describe the post-marketing experience with buspirone in West Germany.

1. <u>Clinically Significant Events</u>:

There were 15 events identified as serious: one death (a probable suicide, involving carbon monoxide poisoning in combination with a multiple drug overdose); three seizures, one of which may have been related to alcohol abuse, and a second described as "petit mal" which was poorly documented; six cardiac events, including three myocardial infarctions (two in patients with histories of coronary artery disease), one case of cardiomyopathy, of unknown cause, a case of syncope in a patient who had a history of orthostatic hypotension, and a case of dizziness/lightheadedness associated with cardiac arrhythmia in a patient with a history of such events prior to buspirone use; one case of autonomic dysfunction (right sided "hypesthesia") in a patient with a history of left hemiparesis and hypesthesia as an infant; two buspirone overdoses, both involving minimal buspirone doses and essentially no untoward effects; one case of viral meningitis; and a depressed patient who became delusional and suicidal.

Because of a concern for the possibility of extrapyramidal symptoms (EPS) occurring with buspirone use (based on buspirone's demonstrated affinity for the dopamine receptor and its weak prolactin elevating effect), the data base was systematically searched for symptoms suggestive of EPS. Although the complaint of tremor did occur in some buspirone patients, it was not typical of neuroleptic induced tremor. There were no clear cases of dystonia. There were four reported cases of akathisia, but all in one study, in which three patients on diazepam were also diagnosed as having akathisia. There were no cases of tardive dyskinesia.

2. Clinical Laboratory Data:

The primary source of clinical laboratory data was the group of approximately 2000 patients in the buspirone clinical development program for whom laboratory data were available. From this group, 20 cases were identified for whom there were laboratory abnormalities of possible clinical significance and possibly causally related to buspirone use.

a. Liver Enzyme Elevations:

Fifteen of these cases involved elevations of SGOT and/or SGPT, which were discovered in the course of routine monitoring, and none of these cases was discontinued for these changes and none developed jaundice.

1. For three patients in long term safety studies (6-12 months), including one with an SGPT of 330 during treatment, enzyme levels had returned to normal at termination, despite continued treatment. A fourth long term patient was noted to have roughly eight-fold elevations in SGOT and SGPT one week after finishing a six month course of buspirone, and while the SGOT had normalized after an additional week, SGPT was 159 (seven times baseline). No follow-up was available.

2. Two patients, who were being treated for alcohol detoxification with buspirone up to 80 mg/day and who had modest enzyme elevations at baseline, were noted to have roughly three-fold elevations after their brief exposures to buspirone. No follow-up was available.

3. Four patients, in short term trials, whose enzyme levels were normal at baseline were noted at termination to have elevations ranging from 3 to 25 times baseline levels. The most prominent increase involved a change in SGOT from 27 at baseline to 576 at termination, and a decrease to 51 within three days of stopping buspirone. Another patient had an increase in both SGOT and SGPT (with the SGPT rising from 50 to 708), but it was noted that this patient had been off buspirone three weeks at the time of sampling, and no follow-up was available. A third patient had a 12-fold increase in both SGOT and SGPT, with both returning to normal within two weeks of stopping buspirone. The remaining patient in this group had a three-fold elevation in SGPT (26 to 88), and follow-up was not available.

4. The five remaining subjects with enzyme increases were participants in a trial to study the potential for an additive effect of buspirone and trazodone on hepatic enzyme increases. This was a crossover study involving 24 healthy males assigned for one week to either buspirone (15 mg t.i.d.) or trazodone (50 mg t.i.d.), followed by a second week of the alternate drug, in combination with the drug given during the first week. Five subjects had increases in SGPT ranging from 3 to 6 times normal. In four of these cases, the initial increase occurred on trazodone, with slight additional increases in two cases and decreases in two other cases after the addition of buspirone. The fifth case had a slight increase in SGPT on buspirone and then a more substantial increase when trazodone was added. The highest SGPT level at any point for these five cases was 273. SGPT levels returned to normal after drug discontinuation for all subjects. None of the subjects had clinically significant increases in other liver enzymes or other laboratory values, or showed any signs or symptoms of clinically significant illness. A follow-up study attempting to further define an interaction was unable to detect any additive effect on hepatic transaminases.

b. <u>WBC</u>:

Three patients experienced decreases in total WBC, although none was discontinued for these changes. One patient treated for three months was noted to have a WBC of 2.1 (differential count not available) one month after stopping buspirone (compared to 6.1 at baseline), with no follow-up available. This patient was also had an increase in eosinophils from 0% at baseline to 14% at five weeks. A second patient with a WBC of 7.0 at baseline was noted to have a WBC ranging from 2.7 to 3.3 (with normal neutrophil count) after roughly 6 to 12 months of treatment, with a return to 7.2 after several months off buspirone. A third patient had a slight decrease from 6.2 to 4.1 after 12 days of treatment (normal neutrophil count).

c. <u>Platelets</u>:

One patient was noted after four weeks of treatment to have a platelet count of 117,000 compared to 303,000 at baseline. A second patient was noted to have a platelet count of 158,000 at one year follow-up compared to 207,000 at baseline. Neither had any other hematological abnormalities, and no follow-up was available.

3. ECG Data:

ECG data were available from 1323 patients who were exposed to buspirone in the clinical program. Of these cases, 183 were reviewed because of the finding of an ECG abnormality during or shortly after buspirone treatment. For 157 of these patients, it was determined that the ECG findings associated with buspirone treatment were of little clinical significance and not substantially different from baseline. Of the 26 remaining cases, 7 had abnormal baseline readings with only minimal change during or after buspirone treatment (including the following baseline abnormalities: bundle branch block, myocardial ischemia, nonspecific S-T segment changes). Fifteen patients had normal baseline readings and subsequent changes of minimal clinical significance (i.e., nonspecific changes in S-T segments or T-waves, junctional rhythm, axis deviation or premature systole). The four remaining cases (two myocardial infarctions, one cardiomyopathy and one patient with lightheadedness and frequent PVCs) have already been discussed under clinically significant events.

4. Vital Signs Data:

Vital signs data were analyzed for 2200 patients taking buspirone at doses in the range proposed for clinical use. Outliers were defined as patients having termination values as follows: HR less than 40 or greater than 140; Systolic BP less than 70 or greater than 175; Diastolic BP less than 50 or greater than 110. There were no outliers for heart rate. There were 27 outliers for blood pressure, including 18 for systolic blood pressure and 9 for diastolic blood pressure, but these were usually patients who had either high or low blood pressure at baseline and whose values for these variables tended to be fairly consistent throughout treatment. There were no individual cases identified with significantly abnormal vital signs values that could be persuasively linked to buspirone use, nor overall trends suggesting patterns of clinically significant alterations in vital signs in association with buspirone use.

5. Discontinuations:

There were 708 patients (out of 3004 patients in the computer data base) who left studies before their targeted endpoints for 1) untoward events, 2) lack of therapeutic effect or 3) intercurrent illness. These were examined to identify patients who had suffered any unusual or unexpected event that might be drug related. No previously unrecognized serious events were detected.

For the 226 anxious patients (out of 2200 participating in clinical trials) who were classified as dropping out for untoward events, a determination was made (where possible) of the primary reason for dropping out. The more common events associated with discontinuation included: CNS disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness and lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, no one of which could be characterized as primary.

6. Side Effects Profile:

Estimates of adverse event incidences are based on data pooled from 17 three-way studies comparing buspirone, diazepam and placebo. These data reflect neither the severity of the reported reaction nor the investigator's judgement of the probability that the event was drug related. Rather, an event was considered to be treatment emergent for any given patient if at any time during treatment that event was present (if absent at baseline) or was present at a severity greater than baseline (if present at baseline). Events listed are primary terms, defined by grouping investigator terms that are similar in meaning.

These estimates of event incidences are necessarily influenced by drug dose, detection technique, setting and physician judgement. Consequently, these incidence figures must be accepted as rather imprecise estimates. They cannot be used to predict the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. Comparison of the cited figures, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Because the doses at which buspirone and diazepam were used in these 17 studies were frequently not equally efficacious, these data cannot provide meaningful comparisons of side effects for the two active drugs. Therefore, the discussion will focus only on a comparison of buspirone and placebo.

Among the more commonly observed untoward events associated with the use of buspirone and not seen at an equivalent incidence among placebo treated patients were: dizziness, nausea, headache, nervousness, lightheadedness, excitement, anger/hostility, confusion, numbness, weakness and diarrhea.

The following table summarizes the treatment emergent adverse experience incidence for buspirone and placebo patients in these 17 three-way trials for events occurring at an incidence of 1% or more in buspirone patients:

Treatment Emergent Adverse Experience Incidence
in Placebo-Controlled Clinical Trials*
(Percent of Patients Reporting)

Adverse Experience	BUSPAR (n=477)	Placebo (n=464)
Cardiovascular		
Tachycardia/Palpitations	1	1
CNS		
Dizziness	12	3
Drowsiness	10	9
Nervousness	5	1
Insomnia	3	3
Lightheadedness	3	-
Decreased Concentration	2	2
Excitement	2	-
Anger/Hostility	2	-
Confusion	2	-
Depression	2	2
EENT		
Blurred Vision	2	-
Gastrointestinal		
Nausea	8	5
Dry Mouth	3	4
Abdominal/Gastric Distress	2	2
Diarrhea	2	-
Constipation	1	2
Vomiting	1	2
Musculoskeletal		
Musculoskeletal Aches/Pains	1	-
Neurological		
Numbness	2	-
Paresthesia	1	-
Incoordination	1	-
Tremor	1	-
Skin		
Skin Rash	1	-
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	-
Sweating/Clamminess	1	-

(*) Events reported by at least 1% of buspirone patients are included.
(-) Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of Buspar:

The following tabulation includes estimates of the overall event rate in the total buspirone population included in the sponsor's computer data base for events occurring at a frequency of less than 1% in the above table, as well as for events occurring in studies other than those included in the above table. During its premarketing assessment, buspirone was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of buspirone in the dose range for which buspirone is being recommended and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to buspirone treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia.

Central Nervous System: Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, slurred speech and psychosis.

EENT: Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on the eyes.

Endocrine: Rare were galactorrhea and thyroid abnormality.

Gastrointestinal: Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue.

Genitourinary: Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia.

Musculoskeletal: Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias.

Neurological: Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness.

Respiratory: Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis.

Sexual Function: Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.

Skin: Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails.

Clinical Laboratory: Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia.

Miscellaneous: Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

7. Long Term Studies:

Two groups of long-term studies with buspirone were designed to look at late occurring side-effects, tolerance or possible withdrawal effects. In one set of studies involving the treatment of patients up to one year, there was no pattern of dose escalation over time. Among 132 patients treated with buspirone for longer than 6 months and then withdrawn, there were no seizures, movement disorders or other important events. However, of 39 U.S. patients in the study, 13 had increases in anxiety upon withdrawal, and 9 of these were placed on benzodiazepine treatment.

The sponsor also provided interim results for study 1345, a double blind, controlled trial to assess the re-emergence of anxiety or withdrawal symptoms in patients with generalized anxiety disorder who initially responded to either buspirone or clorazepate, and then were maintained for 6 months prior to abrupt discontinuation (by placebo substitution) for 3 weeks. Interim results for a total of 40 patients (25 on clorazepate and 15 on buspirone) suggested that, while both groups improved during treatment as measured by HAM-A, only the clorazepate patients had increases in HAM-A scores during the 2 weeks after withdrawal. Clorazepate patients also demonstrated withdrawal symptoms on both the physician and patient rated withdrawal check list, unlike the buspirone patients.

These data provide some reassurance regarding the occurrence of tolerance during long-term use, late occurring side effects and withdrawal symptoms, but the data are preliminary. Also, there is a slight discrepancy with other data, since in the long-term studies, 13 of the U.S. patients withdrawn from buspirone had clinically significant increases in anxiety, while in study 1345 there were apparently no significant increases in anxiety in buspirone patients after withdrawal. There are insufficient data from controlled studies to draw any conclusions about withdrawal symptoms from buspirone at present.

8. Post Marketing Experience in West Germany:

Since the marketing of buspirone in West Germany in March, 1985, there have been 26 ADRs spontaneously reported among an estimated 100,000 buspirone treated patients. None of these cases involved a serious event, but there was a report of akathisia in a patient also receiving prior and concomitant treatment with fluspirilene i.m. (a depot neuroleptic). A second case involved a report of transient dyskinesia. This patient experienced face and neck movements and also pursing of the lips and lip smacking on the second day of buspirone treatment. These movements resolved within 24 hours, but a feeling of restlessness and agitation persisted.

In a four week, open post marketing study in West Germany involving a fixed dose of buspirone (5 mg t.i.d.) in approximately 7000 patients, 25 percent reported at least one ADR, and 436 were discontinued for intolerance. The most frequent ADRs in the discontinued group included: dizziness, gastrointestinal distress, headache, insomnia, vomiting, restlessness. There were no serious events, but there was one report of akathisia in this group, again in a patient taking concomitant fluspirilene i.m.

9. Prolactin Studies in Humans:

Because buspirone has been demonstrated to have a dopamine antagonist effect in preclinical investigations, its effect on prolactin secretion in humans was studied. Dr. Herbert Meltzer conducted a double blind placebo controlled study of prolactin and other hormone levels after single oral doses of buspirone to normal male volunteers (study 1234). Six subjects received single doses of 5, 10 and 15 mg of buspirone, and 8 subjects received single doses of 30, 60 and 90 mg of buspirone. Buspirone at the 60 and 90 mg level produced a dose related increase in prolactin levels 1-3 hours after dosing.

Dr. J. B. Cohn conducted a single blind study of prolactin and other hormone levels during 28 days of buspirone administration to 23 male and female outpatients with generalized anxiety disorder (study 1420). No increase in prolactin was seen during buspirone administration.

Drs. Timo Sepala and Tapio Tanta of the University of Helsinki in Finland conducted a double-blind, randomized crossover study in 10 healthy male subjects, measuring each subject's prolactin response after the following 5 treatments: buspirone 25 mg, buspirone 50 mg, buspirone 100 mg, sulpiride 200 mg and placebo. Among the buspirone dosages, only the 100 mg dose was significantly different from placebo. The 200 mg dose of sulpiride produced the highest prolactin increases and was significantly different from all of the buspirone treatments.

Buspirone at high doses is capable of increasing plasma prolactin levels, but there appears to be considerable individual variation, and the prolactin increases seen are of smaller magnitude than those seen after usual doses of neuroleptics. Although there is no clear evidence for prolactin increases associated with buspirone treatment within the recommended dose range for this drug, the patient samples studied may not have been of adequate size to detect a weak effect.

10. Summary of Safety Issues:

a. Extrapyramidal Side Effects:

Despite the recognized affinity of buspirone for dopamine receptors, and the weak prolactin elevating effect associated with buspirone use, the safety experience with buspirone in the clinical development program and the post marketing experience with buspirone in West Germany do not suggest that typical neuroleptic induced extrapyramidal symptoms are likely to be associated with buspirone use. However, the "restlessness" and "excitement" reported in some buspirone treated patients could have several interpretations, one of which is that these cases represent akathisia. Also, since tardive dyskinesia is a late occurring side effect, it is too early to say whether or not this event is associated with the long-term use of buspirone.

b. Syndrome of Nervousness and Excitement:

A comparison of ADRs between buspirone and placebo patients in data pooled from 17 controlled studies revealed several primary terms occurring more frequently with buspirone than with placebo. Among these terms, nervousness and excitement were most frequently rated as severe, while dizziness and

lightheadedness were most frequently rated as moderate. As noted in the classification of patients discontinued for untoward events, 3.4% of these patients had a clustering of symptoms including dizziness, insomnia, nervousness, drowsiness and lightheadedness. A search for clinically significant events also detected a group of patients who experienced restlessness, tremulousness and other symptoms suggestive of arousal or excitement. There are several interpretations for these findings, including the possibility of akathisia noted above. Other possible interpretations include: 1) an enhancement of benzodiazepine withdrawal effects by buspirone in patients who were withdrawing from prior benzodiazepine treatment~~in~~, and 2) a primary stimulant effect of buspirone in certain patients. The finding of a significantly higher incidence of prior benzodiazepine use in buspirone patients with complaints of restlessness supports the possibility of enhanced benzodiazepine withdrawal. Despite the difficulty in explaining the occurrence of this cluster of symptoms in buspirone treated patients, it does seem to represent a real finding that will require further study.

c. Liver Enzyme Elevations:

Fifteen out of approximately 2000 buspirone treated patients for whom laboratory assessments were available had increases in serum transaminases (SGOT and SGPT) of possible clinical significance, but none developed jaundice and none were discontinued for these changes. Although there were confounding factors that may have contributed to these changes in some cases, buspirone could not be ruled out as a potential contributing factor.

d. Overdose Experience:

There has been a very limited experience of overdosing with buspirone. Only two patients of the 3558 patients in the clinical development program were reported to have taken excessive doses of buspirone. In neither case was the dose excessive and neither experienced any significant untoward effects. There was also complete recovery in three buspirone overdoses occurring in the post marketing experience in West Germany. Thus, the most useful experience regarding excessive dosing with buspirone comes from tolerance studies in normals. In these studies, 375 mg was the maximum tolerated dose. As the maximum dose levels were approached, the most commonly observed symptoms were, nausea, vomiting, dizziness, drowsiness, miosis and gastric distress.

D. Bioavailability

Studies regarding bioavailability/bioequivalence, dose proportionality (single and multiple dose), food interaction, protein binding, metabolism and elimination are summarized below:

1. Bioavailibility/Bioequivalence:

Study 1665 (n=8) compared the bioequivalency of the 5 mg ovoid-rectangular (pillow-shaped) tablet and the 5 mg round tablet. These two formulations were found to be bioequivalent. The ovoid-rectangular tablet is the proposed formulation for marketing. The round tablet formulation is used in all the bioavailability and pharmacokinetic studies listed above.

Study 1261 (n=24) compared the bioavailability of 5 and 10 mg buspirone HCl round tablets to a 0.1% reference solution. Blood samples were assayed for both unchanged buspirone and total immunoreactive metabolites using a radioimmunoassay (RIA). Measurements of unchanged buspirone showed a mean bioavailability (AUC) for buspirone tablets of 66% (5 mg) and 65% (10 mg) of the 0.1% reference solution. The elimination half life of unchanged buspirone was estimated to be 1 to 2 hours. However, when the immunoreactive metabolites were considered, the AUCs of the tablets were 108% (5 mg) and 112% (10 mg) of the 0.1% solution, suggesting the relatively low bioavailability of the tablets was not due to inadequate tablet dissolution or poor absorption from the gastrointestinal tract, but rather, to a greater degree of presystemic metabolism (first pass effect) caused by the different absorption (presumably slower) rates of the tablets. This result suggests that buspirone exhibits nonlinear pharmacokinetics.

2. Dose Proportionality:

The dose proportionality (linearity) of buspirone was studied in a single dose (#1292) and a multiple dose study (#1490). In the single dose study (n=24), 10, 20 and 40 mg doses of buspirone HCl were given as different volumes of a 0.1% solution. The AUC and C_{max} of unchanged buspirone were proportional to the administered doses, and the elimination half life was approximately 2.5 hours. In the multiple dose study (n=15) each subject received a single 20 mg dose (four 5 mg tablets) on Day 1; a 5 mg tid dose (one 5 mg tablet q 8 hr) on Days 2 and 3; a 10 mg tid dose (two 5 mg tablets q 8 hr) on Days 4 and 5; a 20 mg tid dose (four 5 mg tablets q 8 hr) on Days 6 and 7; and a 20 mg single dose (four 5 mg tablets) on day 8. The plasma data showed that steady state was reached during the last three observations (C_{min}) of each dose escalation. The mean unchanged buspirone AUC during the last dosing interval (20 mg dose) at steady state on Day 8 was significantly higher (39%) than the $AUC_{0-\infty}$ on Day 1 after a single 20 mg dose. As in study 1261, this finding suggests there is saturable hepatic metabolism so that higher doses yield more unchanged buspirone. This conclusion is consistent with the finding of a significant increase in unchanged buspirone

elimination half-life (34%) during steady state as compared to that of a single dose. Furthermore, after normalization for dose differences, the mean $C_{ss\ min}$ values of the 20 mg tid dose were significantly higher than that of the 10 mg tid dose which was significantly higher than the mean $C_{ss\ min}$ of the 5 mg tid dose. These results suggest that the pharmacokinetics of buspirone are nonlinear after multiple dosing; in particular, dose increases and repeated dosing may lead to somewhat greater blood levels of unchanged buspirone than would be predicted from single dose studies.

3. Food Interaction:

Study 1439 (n=8) examined the effect of food on the absorption of buspirone tablets (5 mg round tablets). With food, the AUC and C_{max} of unchanged buspirone was found to increase 84% and 116% respectively. The elimination half life of unchanged buspirone was estimated to be 2.2 hours with food and 3.2 hours without food.

4. Protein Binding:

Plasma protein binding of buspirone was studied in vitro using the equilbrium dialysis method. At 1 ng/ml plasma concentration, buspirone is at least 93% bound to plasma protein. The effect of buspirone on the binding of digoxin, dilantin, propranolol and warfarin in human plasma proteins was investigated. Except for digoxin (at the 1 ng/ml level), no significant change in the protein binding of these drugs was found when the concentration of buspirone was less than 100 ng/ml (the plasma buspirone concentrations after therapeutic doses are usually less than 5 ng/ml). However, data regarding the effect of these drugs on the protein binding of buspirone has not been reported.

5. Metabolism and Elimination:

Studies 599 and 1140 examined the absorption, distribution, metabolism and elimination of buspirone in humans using ^{14}C labeled buspirone. Results showed that 29 to 63% of the administered dose was excreted in the urine and 28 to 38% was recovered in the feces. Unchanged buspirone in the plasma between 0 to 24 hours after dosing was about 1% of the total radioactivity, suggesting that buspirone undergoes extensive first pass metabolism.

The sponsor proposed a metabolic scheme for buspirone, suggesting that in man it is metab lized by hydroxylation and oxidative cleavage. In animal studies, a pharmacologically active metabolite, 1-(2-pyramidinyl)-piperazine (1-PP) has been identified. The plasma and brain concentration of 1-PP in the animal study were reported to be about 20 times higher than unchanged buspirone. However, preliminary data from a long-term human safety study of buspirone showed that 1-PP levels were several fold lower than those observed in the animal toxicology studies.

Based on the results of the above studies, human buspirone pharmacokinetics can be described as follows:

a. Buspirone is absorbed and eliminated rapidly in humans after ingestion. Peak plasma concentrations of unchanged buspirone are observed between 40 and 90 minutes.

b. After a single oral dose, circulating plasma buspirone is about 65-66% of that generated by a 0.1% reference solution. The tablet is as completely absorbed as the solution, and the difference appears to be circulating inactive metabolites resulting from presystemic metabolism for the tablet formulation.

c. Between 15 mg to 60 mg daily dose, the pharmacokinetics of buspirone appear to be nonlinear after oral multiple dosing, with relatively increased blood levels at the higher doses.

d. Food increases the bioavailability of unchanged buspirone.

e. In man, approximately 95% of buspirone is bound to plasma protein.

f. After a single ^{14}C dose, 29% to 63% of the radioactivity is excreted in the urine within 24 hours as metabolites. Fecal excretion accounts for 28 to 38% of the radioactivity. Unchanged buspirone in the plasma (0-24 hours) represented only 1% of the total radioactivity, suggesting that buspirone undergoes extensive metabolism.

g. The elimination half life of unchanged buspirone after single dosing is about 2 to 3 hours.

E. Drug Abuse Evaluation:

BUSPAR has shown no potential for drug abuse and dependence based on human and animal studies. Human volunteers with a history of recreational drug or alcohol usage were used in two double-blind clinical studies. None of the subjects were able to distinguish between BUSPAR and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats, have indicated that BUSPAR lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of BUSPAR did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that BUSPAR causes physical dependence or drug seeking behavior, it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BUSPAR misuse or abuse (e.g., development of tolerance, incrementation of dose, drug seeking behavior, etc.)

VI. Pertinent Advisory Committee Minutes.

The Psychopharmacologic Drugs Advisory Committee met on September 22, 1984. The committee made a number of recommendations. All recommendations were unanimous, (8-0), and were as follows:

1. Data obtained from adequate and well controlled clinical trials demonstrate that buspirone is an effective and acceptably safe anxiolytic agent in patients with Generalized Anxiety Disorder.

2. The Committee was unable to conclude that buspirone has a distinct antidepressant effect beyond that usually associated with effective anxiolytics in the population studied (i.e., those with generalized anxiety).

3. The Committee supports the Division's plan to require a statement in the product's labeling about the possible risk factors associated with buspirone's effects on dopamine metabolism.

It should be noted that the Psychopharmacologic Drugs Advisory Committee was not aware at the time of this meeting of the problems later discovered in three of the five placebo controlled studies cited as providing a basis for the anxiolytic efficacy of buspirone (i.e., the two Goldberg studies and the Rickels study). However, as noted in section "A", the Rickels study was reanalyzed excluding the questionable data and was still found to be a strong source of support for the anxiolytic efficacy of buspirone, as was an additional placebo controlled study (i.e., Bohm).

VII. Conditions for Approval.

Phase IV conduct of (1) a multiple dose bioavailability study comparing the 5mg and 10mg round tablets with a reference solution in which both unchanged buspirone and 1-PP plasma levels are determined, (2) an in vitro protein binding study to determine the effect of highly protein bound drugs on the protein binding of buspirone, and (3) a study to prospectively explore an apparent differential responsiveness to buspirone among anxious patients with and without prior benzodiazepine treatment.

VIII. Approved Package Insert.

The draft package insert is attached.

cc:
Orig:NDA
HFN-120
HFN-120/PLeber/TLaughren/KKook/FVocci
JContrera/RShultz/FZinsitz/TDeCicco
ad/rd/2/4/85/9/19/86
ft/pjd/6/27/86
Revised/TLaughren/10/20/86
ft/pjd/10/20/86
DOC#02621

R. Temple 11/3/86

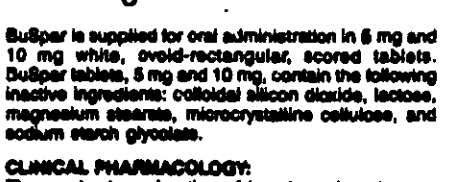
PZ

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

BUSPAR®
(buspirone HCl)

DESCRIPTION:
BuSpar® (buspirone hydrochloride) is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.

Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione monohydrochloride. The empirical formula $C_{21}H_{31}N_5O_2 \cdot HCl$ is represented by the following structural formula:



BuSpar is supplied for oral administration in 5 mg and 10 mg white, ovoid-rectangular, scored tablets. BuSpar tablets, 5 mg and 10 mg, contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY:
The mechanism of action of buspirone is unknown. Buspirone differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. *In vitro* preclinical studies have shown that buspirone has a high affinity for serotonin ($5\text{-}HT_{1A}$) receptors. Buspirone has no significant affinity for benzodiazepine receptors and does not affect GABA binding *in vitro* or *in vivo* when tested in preclinical models.

Buspirone has moderate affinity for brain D_2-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

BuSpar is rapidly absorbed in man and undergoes extensive first pass metabolism. In a radiolabeled study, unchanged buspirone in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects. Peak plasma levels of 1 to 6 ng/ml have been observed 40 to 90 minutes after single oral doses of 20 mg. The single dose bioavailability of unchanged buspirone when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of BuSpar have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116% respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone, but the clinical significance of these findings is unknown.

A multiple dose study conducted in fifteen subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single dose studies.

In man, approximately 95% of buspirone is plasma protein bound, but other highly bound drugs, e.g., phenytoin, propranolol and warfarin are not displaced by buspirone from plasma protein *in vitro*. However, *in vitro* binding studies show that buspirone does displace digoxin.

Buspirone is metabolized primarily by oxidation producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinyl piperazine (1-PP). In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to BuSpar do not exhibit high levels of 1-PP; mean values are approximately 3 ng/ml and the highest human blood level recorded among 106 chronically dosed patients was 17 ng/ml, less than 1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.

In a single dose study using ^{14}C labeled buspirone, 29 to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18 to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is about 2 to 3 hours.

The pharmacokinetics of BuSpar in patients with hepatic or renal dysfunction has not been determined, nor has the effect of age. The effect of BuSpar on drug metabolism or concomitant drug disposition has not been investigated.

INDICATIONS AND USAGE:
BuSpar is indicated for the management of anxiety disorders or the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of every day life usually does not require treatment with an anxiolytic.

The efficacy of BuSpar has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (300.02) of the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as described below:

Generalized, persistent anxiety (of at least one month continual duration), manifested by symptoms from three of the four following categories.

1. Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.
2. Autonomic hyperactivity: sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, light-headedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.
3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.
4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge," irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia.

The effectiveness of BuSpar in long term use, that is, for more than three to four weeks, has not been demonstrated in controlled trials. However, patients have been treated with BuSpar for several months without ill effect. Therefore, the physician who elects to use BuSpar for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS:
BuSpar is contraindicated in patients hypersensitive to buspirone hydrochloride.

WARNINGS:
Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General:
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that is does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., cystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
To assure safe and effective use of BuSpar, the following information and instructions should be given to patients:

1. Inform your physician about any medications, prescription or non-prescription, alcohol or drugs that you are now taking or plan to take during your treatment with BuSpar.
2. Inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking BuSpar.
3. Inform your physician if you are breast feeding an infant.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.

Laboratory Tests:
There are no specific laboratory tests recommended.

Drug Interactions:
Because the effects of concomitant administration of BuSpar with most other psychotropic drugs have not been studied, the concomitant use of BuSpar with other CNS active drugs should be approached with caution.

There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins. However, it may displace less firmly bound drugs like digoxin; the clinical significance of this property is unknown.

Drug/Laboratory Test Interactions:
Buspirone is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats during a 24-month study at approximately 133 times the maximum recommended human oral dose; or in mice, during an 18-month study at approximately 167 times the maximum recommended human oral dose.

With or without metabolic activation, buspirone did not induce point mutations in 5 strains of *Salmonella typhimurium* (Ames Test) or mouse lymphoma L5178YTK$^{+/-}$ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.

Pregnancy: Teratogenic effects:
Pregnancy Category B: No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well controlled studies during pregnancy have *not* been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:
The effect of BuSpar on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

Nursing Mothers:
The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. BuSpar administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness of BuSpar have not been determined in individuals below 18 years of age.

Use in the Elderly:
BuSpar has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with BuSpar without any special adjustment for their age. No unusual adverse age-related phenomena have been identified.

Use in Patients with Impaired Hepatic or Renal Function:
Since BuSpar is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also PRECAUTIONS):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo treated patients include dizziness, nausea, headache, nervousness, lightheadedness and excitement.

Associated with Discontinuation of Treatment:
One guide to the relative clinical importance of adverse events associated with BuSpar is provided by the frequency with which they caused drug discontinuation during clinical testing. Approximately ten percent of the 2200 anxious patients who participated in the BuSpar premarketing clinical efficacy trials in anxiety disorders lasting three to four weeks discontinued treatment due to an adverse event. The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness and light-headed feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
The table that follows enumerates adverse events that occurred at a frequency of 1% or more among BuSpar patients who participated in four week, controlled trials comparing BuSpar with placebo. The frequencies were obtained from pooled data for seventeen trials. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. Comparison of the cited figure, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	BuSpar (n = 477)	Placebo (n = 464)
Cardiovascular		
Tachycardia/Palpitations	1	1
CNS		
Dizziness	12	3
Drowsiness	10	9
Nervousness	5	1
Insomnia	3	3
Light-headedness	3	—
Decreased Concentration	2	2
Excitement	2	—
Anger/Hostility	2	—
Confusion	2	—
Depression	2	2
EENT		
Blurred Vision	2	—
Gastrointestinal		
Nausea	8	5
Dry Mouth	3	4
Abdominal/Gastric Distress	2	2
Diarrhea	2	—
Constipation	1	2
Vomiting	1	2
Musculoskeletal		
Musculoskeletal Aches/Pains	1	—
Neurological		
Numbness	2	—
Paresthesia	1	—
Incoordination	1	—
Tremor	1	—
Skin		
Skin Rash	1	—
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	—
Sweating/Clamminess	1	—

*Events reported by at least 1% of BuSpar patients are included.
—Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of BuSpar:
During its premarketing assessment, BuSpar was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of BuSpar in the dose range for which BuSpar is being recommended (i.e., the modal daily dose of BuSpar fell between 10 and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to BuSpar varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to BuSpar treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the PRECAUTIONS section.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular:
Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia.

Central Nervous System:
Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.

EENT:
Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.

Endocrine:
Rare were galactorrhea and thyroid abnormality.

Gastrointestinal:
Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue.

Genitourinary:
Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia.

Musculoskeletal:
Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias.

Neurological:
Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness.

Respiratory:
Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis.

Sexual Function:
Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.

Skin:
Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails.

Clinical Laboratory:
Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia.

Miscellaneous:
Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

NON-DOMESTIC POST-MARKETING EXPERIENCE:
Foreign post-marketing experience has shown an adverse experience profile similar to that given above and no other unexpected adverse reactions have been reported to date.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
In human and animal studies, buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. Human volunteers with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between BuSpar and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that BuSpar causes physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BuSpar misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
In healthy normal human subjects, the maximum tolerated therapeutic dose of BuSpar is 375 mg/day. As the maximum dose levels were approached, the most commonly observed symptoms were: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage of BuSpar. Toxicology studies of buspirone yielded the following LD_{50} values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160-650 times the recommended human daily dose.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.

DOSAGE AND ADMINISTRATION:
The recommended initial dose is 15 mg daily (5 mg three times a day). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20-30 mg per day were commonly employed.

HOW SUPPLIED:
BuSpar (buspirone hydrochloride)

Tablets, 5 mg and 10 mg (white, ovoid-rectangular with score, MJ logo, strength and the name BuSpar embossed) are available in bottles of 100.

NDC 0087-0818-41 Bottles of 100
5 mg tablet

NDC 0087-0819-41 Bottles of 100
10 mg tablet

Store at temperatures below 86°F (30°C).

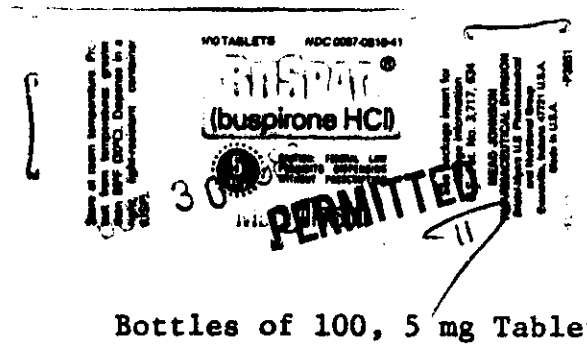
REFERENCE
1. Williams, JWB, Ed.: Diagnostic and Statistical Manual of Mental Disorders — III, American Psychiatric Association, May 1980.

Mead Johnson
PHARMACEUTICAL DIVISION
Evansville, Indiana 47721 U.S.A.

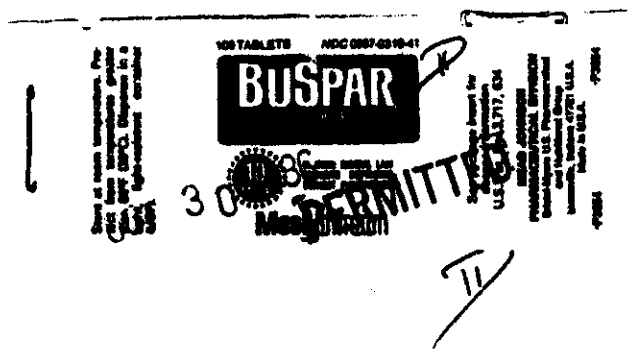
FPL

18-731 10-14-86 D 24947

THIS PAGE CONTAINS CONTAINER LABELS FOR BUSPAR TABLETS



Bottles of 100, 5 mg Tablet
P 3851



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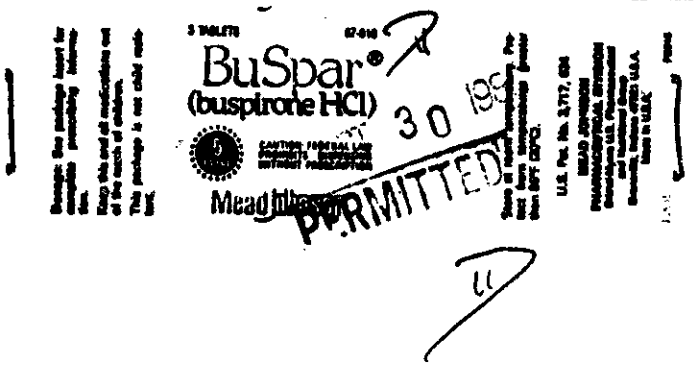
P 3854



Samples Bottles of 3, 5 mg Tablet
P 2615

18-731 10-14-86 D 24948

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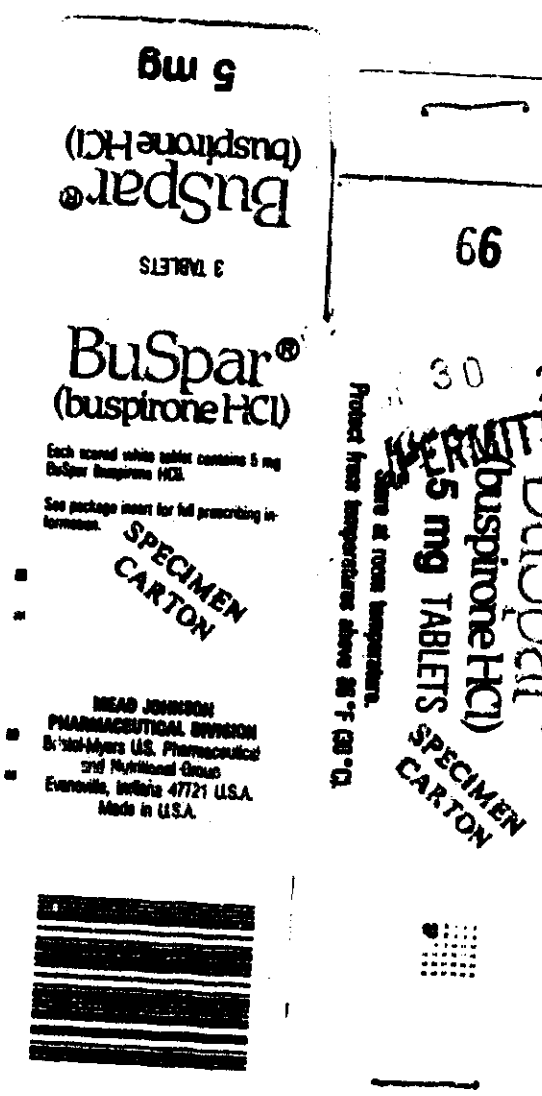
OF 3, 5 mg TABLET



Buspar, 5 mg Tablets, P 2616

66

87-818 3 TABLETS

BuSpar®
(buspirone HCl)

5 mg

CAUTION: FEDERAL LAW
PROHIBITS DISPENSING
WITHOUT A PRESCRIPTION

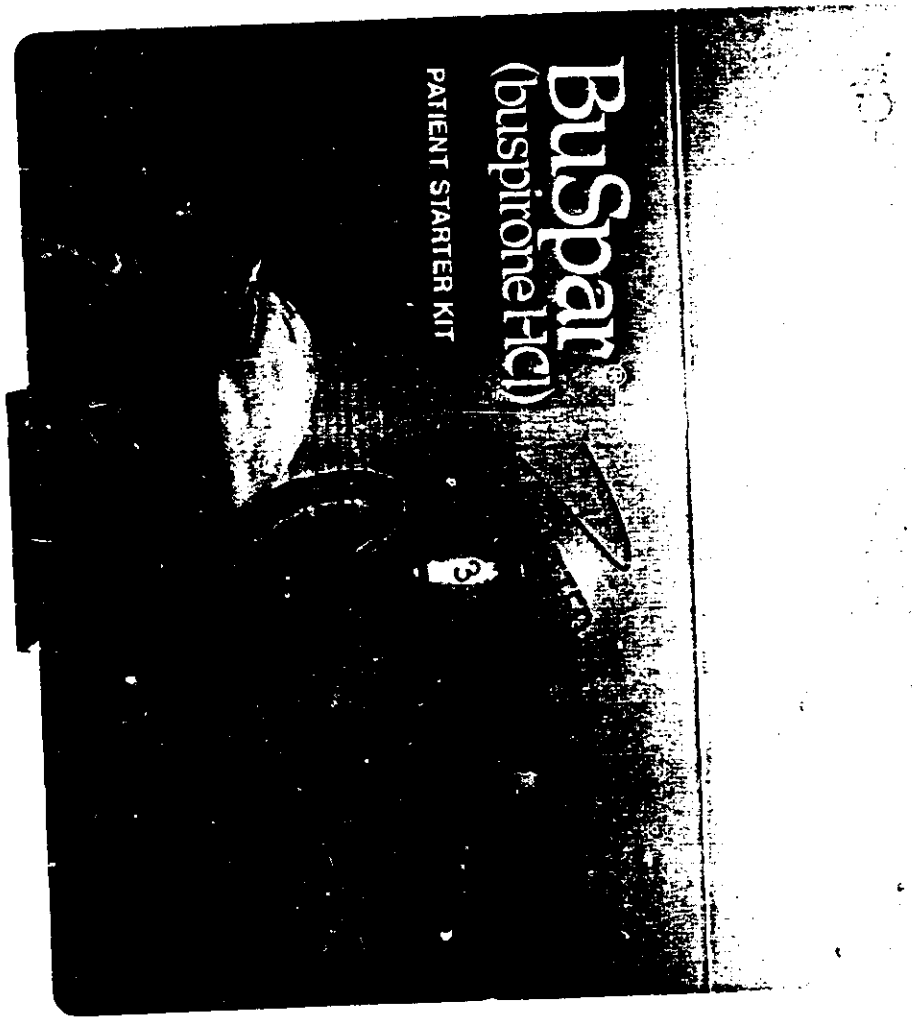
SPECIMEN CARTON

Mead Johnson

BuSpar®
(buspirone HCl)
5 mg TABLETS

SPECIMEN CARTON

P2616
P2616



Mead Johnson
PHARMACEUTICAL DIVISION

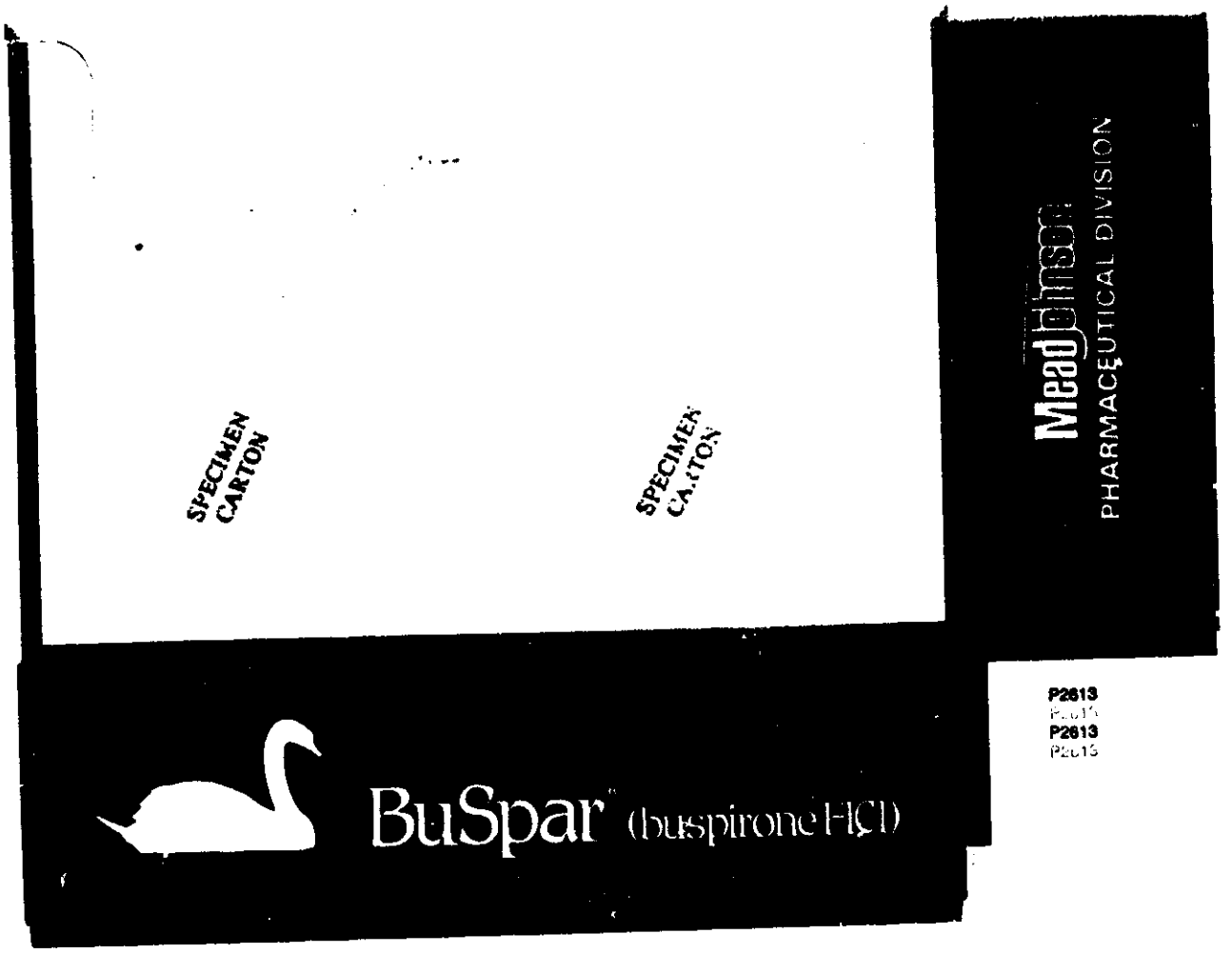
SPECIMEN CARTON

SPECIMEN CARTON

Your BuSpar® Starter Kit includes:

- A Patient Information Booklet which provides valuable information about BuSpar, the drug your doctor has prescribed for you. In this booklet, you will find answers to many of your questions.
- Two Sample Bottles of BuSpar which provide you with medication for about two days, depending on how your doctor has directed you to take it. You can begin your BuSpar therapy immediately, and have your pharmacist fill your prescription at the earliest opportunity.

As with any medication, if you have any questions or problems, consult your physician.



P2613
P2613

MED REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

DATE: October 2, 1986

FROM: Thomas P. Laughren, M.D.
Group Leader, Psychiatric Drug Products Group
Division of Neuropharmacological Drug Products, HFN-120

SUBJECT: Ammendment to NDA 18-731, dated September 29, 1986, regarding FPL for Buspar.

TO: File, NDA 18-731

Mr. Tony DeCicco has done a line-by-line comparison of the FPL presented in the September 29 amendment with the labeling included in our approval letter (dated September 29, 1986). He noted only two changes, one involving a slight change in the wording in the ADR section (a change of "premarketing controlled clinical trials" to "premarketing clinical efficacy trials") and a minor change in the Overdose section (a change of the word "sign" to "symptom"). Both changes are acceptable, but the change in the ADR section alerted me to an error that should be corrected.

The sentence including the above change in the ADR section goes on to indicate that these trials were conducted in patients with "anxiety disorders lasting three to four weeks." In the first place, this is confusing, since it is unclear if this refers to the duration of the anxiety or to the studies. This was intended to refer to study duration. However, it is partly in error, since approximately one third of the patients among the 2200 patients were involved in long term studies. Therefore, I suggest the following wording as an alternative:

> Approximately 10% of the 2200 anxious patients who participated in the Buspar premarketing clinical efficacy trials discontinued treatment due to an adverse event. These were mostly three to four week studies, but also included approximately 700 patients in long term studies.

The sponsor should be notified of this error and asked to make the above change (or suggest an alternative) for the approved labeling for Buspar (or this could be done at the next printing).

Thomas P. Laughren 10-6-86
Thomas P. Laughren, M.D.

cc: Orig.NDA
HFN-120
HFN-120/TLaughren/10/2/86
/TDeCicco
rd/ft/pjd/10/6/86
doc 0641k

Sponsor: Bristol Myers

Drug: buspirone

Drug Category: Anxiolytic

Material Submitted: Information package for a meeting between Bristol Myers and FDA on August 29, 1986.

Correspondence Date: August 20, 1986

Contents of Package:

1. Tables of changes in HAM-D scores

   The sponsor provided this information in support of a request that buspirone be indicated for "anxiety and anxiety associated with depressive symptoms." It should be noted that this is not new information, and we rejected this claim as pseudospecific, since we believe that depressive symptoms are common in association with a primary diagnosis of generalized anxiety disorder and would not be expected to influence the anxiolytic efficacy of buspirone or any other anxiolytic.

2. Reports on the effects of buspirone in patients with Parkinson's disease

   The sponsor provided two reports on buspirone use in patients with Parkinson's disease. Buspirone was not beneficial in the treatment of Parkinsonian symptoms at anxiolytic doses, but was well tolerated at these doses. However, several patients experienced a worsening of Parkinsonian symptoms at higher doses of buspirone (approximately 100 mg/day). It was suggested that this could be explained on the basis of the noradrenergic effects of buspirone, or possibly a dopamine inhibitory effect.

3. Interim report on the long term safety and efficacy of buspirone

   This report concerns 700 patients participating in 12 open-label studies of buspirone in the treatment of generalized anxiety disorders for up to 12 months. At the time of the report, 240 patients had been treated for 6 months, and 106 for 12 months. The sponsor provided this report to support the statement in the labeling regarding the safety of the long term use of buspirone. It should be noted that this report is dated March 27, 1986. I requested and received assurance from the sponsor (September 4, 1986) that all safety data in this report were previously included in the two safety updates already submitted (January, 1986 and August, 1986). The findings of this report are consistent with the findings already noted. Therefore, I did not review this report in detail.

Thomas P. Laughren 9-15-86

Thomas P. Laughren, M.D.

cc: Orig NDA
HFN-120
HFN-120/TLaughren
rd/pjd/9/5/86:ft/9/15/86
doc 0626k

120

SEP - 8 1986

Review and Evaluation of Clinical Data
NDA 18-731

Sponsor: Bristol Myers

Drug: Buspar (buspirone)

Drug Category: Anxiolytic

Material Submitted: Supplementary safety information on previously exposed subjects as well as on new patients exposed to buspirone since December 1, 1985 (the cut-off date for the January 22, 1986 safety update). The cut-off date for this current report is July 21, 1986.

Correspondence Dates: August 22, 1986 and August 28, 1986

Dates of Receipt: August 25, 1986 and August 29, 1986

Population:

The major focus of this safety report is on data obtained for patients in the Bristol Myers Pharmaceutical Research and Development Division (BM-PRDD) studies, including 347 new patients and 230 previously reported patients (for whom new data have been accumulated). The sponsor has also included additional data from phase IV studies in other post-marketing experience in and phase I and II studies in.

Serious Medical Events:

Only two additional serious medical events have been reported among BM-PRDD patients, including one case of viral meningitis (1693/158), which resulted in recovery without sequalae, and a patient (1668/4) in an open depression study with moderately severe depression at baseline who failed to improve and became delusional and suicidal. She subsequently did well on thiothixene and later imipramine. Neither event could, in my view, be reasonably attributed to buspirone treatment.

Overall Adverse Event Summary:

The sponsor has updated the overall event rate tabulation by including additional data from previous patients as well as for 266 new patients (i.e., the present total is N=3004 patients for this database). This reanalysis resulted in several changes in frequency rates and several newly reported events. Case records for newly reported events and reports of other events (previously reported but of special interest) were reviewed by CNS research physicians. No evidence of significant cardiovascular, neurological, drug hypersensitivity, hematologic or endocrine events could be attributed to buspirone treatment. This updated overall event rate tabulation will be incorporated into the labeling for buspirone (agreed to at August 29, 1986 meeting with sponsor).

Discontinuations:

This analysis was conducted in a similar matter for new discontinuations as was done for the original safety update. This procedure is described in detail in my review dated March 18, 1986. In summary, this approach included a focus on patients discontinued for untoward events, intercurrent illness or lack of treatment efficacy. The search was conducted using a subset of critical primary terms and resulted in 85 patients who were discontinued for the above reasons being selected for case report form review by physicians. Only 4 patients were judged to have clinically important events: two have already been identified above in the serious events search (see above section); a third patient with chronic atrial fibrillation was discontinued after developing breathing difficulties while vacationing at a high altitude; a fourth patient was discontinued after developing premature ejaculation. Case report forms and medical summaries were provided for these four patients.

The sponsor included updated ADR incidence tables for discontinued patients. It should be noted that there were no important changes in the frequencies of ADR's in these updated tables compared to the original tables.

The sponsor indicated that there were essentially no changes in the percentages of patients falling into the various categories of patients classified by primary reason of dropping out. This was noted at our meeting with the sponsor on August 29, 1986, and the original classification will be included in the labeling for buspirone.

Laboratory Data:

The analysis of additional laboratory data focused on 448 patients with laboratory tests in the BM-PRDD sponsored studies (it was not clear how many of these were new cases and which were previously reported patients with additional findings). This search was also done in the same manner as the previous laboratory data search. In summary, laboratory parameters in four areas (hypatic, renal, hematologic and metabolic) were identified as important, and then abnormalities meeting certain criteria (see my previous review dated March 18, 1986) were selected for case report form review. The review was two-tiered as before, the first being by non-medical personnel and the second being by medical staff. Physicians looked at all cases where the "worst" or "endpoint" value was worse than baseline, and also at cases with abnormal follow-up values, but without any baseline values. This search resulted in the identification of 6 patients with findings judged possibly clinically significant and/or abnormalities possibly related to buspirone use. Case report forms and medical summaries were provided for these 6 patients. The sponsor's table 10 summarizes these findings:

TABLE 10

Clinically Significant Laboratory Abnormalities
August 1986 Buspirone Safety Update

		Test Values		
Study No. - Pt No.	Test	Baseline	Intermediate	End of Treatment
1856 (D01-4)	SGPT	32	237	34
	SGOT	31	115	31
1856 (D055)	SGPT	23	330	13
	SGOT	14	304	35
	ALP	119	196	69
1693 (183)	SGOT	43	118	43
	SGPT	31	140	37
1693 (95)	WBC	7	3, 3.3, 2.7	7.2
1345 (51)	WBC	6.2	-	4.1
1693 (129)	Platelets	207,000	287,000	158,000

Three of the six cases involved rather marked increases in SGOT and SGPT (as high as eight times the upper limit of normal in one case). However, all involved long term cases who continued on buspirone despite these findings. There was no other clinical evidence of hepatic injury and all three cases had essentially normal liver function values at the final visit. Alcohol abuse may have been a factor in two of these cases.

Two of the six cases involved a decrease in total WBC. One of these cases involved a female patient taking multiple other drugs in addition to buspirone. Her total WBC dropped from 7.0 at baseline to 3.0 at 6 months. However, she continued on buspirone until the end of the 1 year study. Her WBC was still relatively low even several months after stopping buspirone. However, after several additional months it returned to normal. The other patient discontinued buspirone after 12 days due to headache, drowsiness and nausea. The WBC had dropped from 6.2 to 4.1. There was no follow up on this patient.

Finally, a patient who had been treated with buspirone for one year was noted at the final visit to have a platelet count of 158,000. This was down from 287,000 at six months, and the baseline value had been 207,000. There were no other clinical or laboratory abnormalities in this patient.

The sponsor provided a separate presentation of study 2174 a follow up to earlier study 1973 which was supposed to examine the potential effects of buspirone and trazodone together on liver enzyme elevation. I discussed the findings of the study in my March 18, 1986 review. Briefly, this earlier study involved 24 normal males, who were divided into two groups. One group received buspirone the first week (5 mg tid), and trazodone (50 mg tid) was added to the buspirone during the second week. The second group trazodone alone the first week and then trazodone plus buspirone the second week. In summary, five patients had 3-6 fold elevations in SGPT. Four of these patients were treated initially with trazodone, and had elevations that were either maintained above normal (in two cases) or increased even further (in two cases) with the addition of buspirone. A fifth patient had a very slight increase in SGPT during initial treatment with buspirone, and then a more substantial elevation with the addition of trazodone.

The ____ study was designed to clarify the findings of the ____ study. It was similar to the ____ study, i.e., it utilized the same drugs, doses and number of subjects. However, there were different rules for assigning medications. Subjects began with either drug alone, and if they had no increases in liver enzymes, the second drug was added. If there were still no increases, they were considered to be completed. If either drug alone caused an increase during the first week, they were to continue on that drug for the second week. They were then to be rechallenged with that drug after a washout period. If the increase occurred during the second week when the second drug had been added, they were to continue for a third week on that combination and then were to be rechallenged with that second drug after a washout period. Nine of the twelve patients who started with buspirone and had buspirone plus trazodone during the second week experienced no increase in hepatic enzymes. Similarly, six of the twelve subjects treated first with trazodone and then trazodone plus buspirone had no enzyme elevations. The remaining patients had an increase in hepatic enzymes at some point, but in no case was it greater than approximately twice normal levels. Two subjects had a slight increase on buspirone during the first week. One of these subjects had a continued slight elevation during the second week but the other subject was stopped when it was noted that his hepatic enzymes had been slightly increased at baseline. Four subjects had slight increases while taking trazodone during the first week. One of these was noted to have had elevations at baseline, one returned to normal during the second week, and two had continued elevations during the second week, with positive rechallenge. Two subjects had elevations on the combination of buspirone plus trazodone after starting on buspirone. It turned out that one of these patients had, in fact, had an increase on buspirone alone and had no further increase after the addition of trazodone. The second subject had a slight increase on buspirone plus trazodone, but was noted to have a positive rechallenge with trazodone alone. Two subjects had elevations on buspirone plus trazodone after starting on trazodone. Unfortunately, no SGPT's were available for the visit just prior to starting buspirone plus trazodone. In any case, despite the slight increase in enzymes, both returned to normal during continued combination treatment.

The sponsor concludes that there is no basis for believing that there is an additive interaction on hepatic enzyme elevation with the combination of buspirone and trazodone. Rather, the sponsor notes that both drugs have a slight potential for increasing transaminases. I am inclined to agree with this assessment, although I think the data are simply to sparse to disprove an interaction. In any case, in our August 29, 1986 meeting with the sponsor regarding labeling for this product, we agreed on a modified statement in the drug interaction section which acknowledges the initial finding but notes that it was not replicated in the follow up study. I believe that this statement is consistent with the data.

Additional Data from Foreign Sources:

Bristol Myers has initiated 21 phase IV studies in 9 foreign countries, and reports here on data from 5 such studies in Preliminary data were available from 251 patients in four of these studies. Thirty-seven of the 251 patients were discontinued. The complaints in these patients were typical of other buspirone discontinuations, i.e., most commonly dizziness, gastrointestinal, headache and sleep disturbance. None of these involved serious events. Also, there were additional data from 477 patients in the large phase IV field study in Eighty-seven (18.2%) of these patients reported ADR's, including 27 who discontinued for ADR's (apparently none being serious or unusual).

The sponsor also reports that approximately 100,000 patients have now been treated with buspirone in West Germany (compared to 40,000 at the last report). Thirteen additional spontaneous reports of ADR's have been noted for these patients, as follows:

1. Torticollis (stiff neck)
2. Ataxia, slurred speech
3. Headache
4. Withdrawal symptoms
5. Acute organic brain syndrome
6. Hypertension and tachycardia
7. Sleeplessness, urinary urgency, difficulties with motor coordination
8. Elevated hepatic liver enzymes
9. Sleep disturbance
10. Attempted suicide
11. Colic
12. Drug dependency
13. Drug dependency

The sponsor includes a brief discussion of the more important events in this list. Apparently, the report of torticollis was more appropriately labeled a stiff neck, but apparently this did remit after discontinuation of buspirone. The case involving ataxia and slurred speech apparently involved a patient who was intoxicated with alcohol. Case #4 (labeled withdrawal symptoms) involved a patient who had withdrawal symptoms after stopping buspirone, but who also apparently experienced "withdrawal symptoms" after stopping placebo. Case #5 (acute organic brain syndrome) apparently involved a patient who was intoxicated with alcohol. The case of hypertension and tachycardia (#6) involved a 59 year old woman with concurrent ASHD, hypertension and diabetes who was being treated with multiple other medications, but who apparently did experience three episodes of severe palpitations and flushing, with elevated blood pressure, one week after starting buspirone. The episodes apparently subsided spontaneously. The report of elevated hepatic liver enzymes (#8) involved a 64 year old man who was also being treated with multiple other medications. The enzyme elevations were only slightly abnormal, with an SGPT of 27 and an SGGT of 59.

The sponsor has also received preliminary information on 289 patients treated in phase I and phase II studies in There have been no deaths or serious medical events among these patients. The only two cases of possible significance involved patients with mild elevations (less than twice normal) of hepatic enzymes.

Conclusions and Recommendations:

This safety update reveals no new adverse events of concern and no change in frequency of adverse events. The sponsor has agreed to make several minor modifications of the labeling for buspirone at our August 29, 1986 meeting, in keeping with the information obtained from this update. No other action is indicated on the basis of this safety update.

Thomas P. Laughren 9-4-86

Thomas P. Laughren, M.D.

cc: Orig.NDA
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JUL - 7 1986

Review and Evaluation of Clinical Data
NDA 18-731

Sponsor: Bristol Meyers

Drug: Buspar (buspirone)

Drug Category: Anxiolytic

Material Submitted:

Additional analyses of efficacy data for selected studies in the NDA, based on stratification of patients regarding prior benzodiazepine use.

Correspondence Dates:

1. June 17, 1986
2. June 19, 1986

Background:

These analyses were requested from the sponsor because of a published report regarding the study (994) in the New England Journal of Medicine (Volume 314, pp. 719-720, 1986) suggesting that patients without prior exposure to benzodiazepines had a better response to buspirone than patients with prior benzodiazepine treatment. We thought that these analyses might help in explaining the negative outcome for buspirone in several of the studies conducted for this drug.

Summary of Data Submitted:

The sponsor conducted analyses for three studies: .994), .(2044), (1802). Data for the subgroup analyses of the remaining three studies were not submitted since the outcomes were less consistent, a finding the sponsor attributed to the fact that most patients in these studies had prior benzodiazepine treatment. Intent-to-treat (last observation carried forward) analyses at weeks three and four and observed cases analyses (at weeks three and four) were done for selected efficacy variables. The statistical methods included analysis of variance for change from baseline for the quantitative variables and generalized approaches for the categorical (global) variables. All statistical tests were two-sided.

The original submission (June 17, 1986) had several deficiencies, i.e., two critical efficacy variables (the HAM-A anxious mood and tension items) were omitted, and also placebo patients were pooled (rather than stratified) in the HAM-A comparisons. These deficiencies were corrected in the June 19, 1986 submission.

This review will focus on the intent-to-treat data for the HAM-A total score, anxious mood and tension items, and for the global psychopathology score from the Physician's Questionnaire.

1. Study #994 ——

The following table displays the p-values for the pairwise comparisons of active drug subgroups with placebo subgroups for the key efficacy variables:

Treatment Group	Prior Benzodiazepine Treatment (n)	Week 3 HAM-A Total	Anx	Tens	P.G. Global	Week 4 HAM-A Total	Anx	Tens	P.G. Global
buspirone	0 (32)	<.001	<.001	.001	<.001	<.001	<.003	.001	.001
	+ (32)	.007	<.021	.001	.008	.015	<.013	.001	.004
diazepam	0 (37)	<.001	<.004	.001	<.001	<.001	<.020	.004	.016
	+ (22)	<.001	<.002	<.001	.001	<.001	<.001	<.001	<.001

While all subgroups were statistically superior to placebo on these measures at both three and four weeks, the buspirone treated subgroup without prior benzodiazepine treatment was more significantly superior in most cases than the subgroup of buspirone treated patients with prior benzodiazepine exposure. In the diazepam treated patients, the subgroup with prior benzodiazepine treatment tended to be more significantly superior to placebo than the subgroup without prior benzodiazepine exposure (although, again, both subgroups were statistically superior to placebo).

2. Study 2044 ——

The following table displays the p-values for the pairwise comparisons of active drug subgroups with placebo subgroups for the key efficacy variables:

Treatment Group	Prior Benzodiazepine Treatment (n)	Week 3 HAM-A Total	Anx	Tens	P.G. Global
buspirone	0 (14)	<.001	<.001	.001	.013
	+ (6)	<.001	.058	.006	.091
diazepam	0 (11)	<.001	.001	.002	.032
	+ (9)	<.001	.003	.001	.001

The findings for these subgroup analyses were similar to those for the ____ study, in that for both active drugs the subgroups were both statistically superior to placebo. However, as in the ____ study, buspirone treated patients without prior benzodiazepine treatment tended to be more responsive to buspirone than those with prior benzodiazepine treatment, while for diazepam treated patients, there was a suggestion that those with prior benzodiazepine treatment were more responsive to diazepam than those without.

3. Study 1802 (Pecknold)

The following table displays the p-values for the pairwise comparisons of active drug subgroups with placebo subgroups for key efficacy variables:

Treatment Group	Prior Benzodiazepine Treatment (n)	Week 3 HAM-A Total	Week 3 HAM-A Anx	Week 3 HAM-A Tens	Week 3 P.G. Global	Week 4 HAM-A Total	Week 4 HAM-A Anx	Week 4 HAM-A Tens	Week 4 P.G. Global
buspirone	0 (10)	.017	.231	.481	.062	.033	.149	.136	.022
	+ (12)	.670	.740	.246	.874	.594	.920	.584	.538
diazepam	0 (11)	.025	.075	.120	.019	.102	.308	.158	.019
	+ (10)	.082	.418	.076	.488	.032	.087	.101	.454

Unlike the and subgroup analyses, these analyses did not consistently demonstrate statistical superiority over placebo for either the buspirone or diazepam subgroups. Nevertheless, there was at least a trend (numerical) for the buspirone treated patients without prior benzodiazepine treatment to fare better relative to placebo than the buspirone treated patients with prior benzodiazepine treatment. The influence of prior benzodiazepine exposure on response to diazepam was less clear from these analyses.

Conclusions and Recommendations:

While these post hoc, subgroup analyses are primarily of value in generating hypotheses for further testing, they do suggest that prior benzodiazepine exposure might influence responsiveness to buspirone treatment, i.e., patients without prior benzodiazepine treatment may respond more positively to buspirone than patients with prior benzodiazepine treatment. The significance of this finding is unclear. It could mean that anxious patients who have had prior benzodiazepine exposure have come to expect the sedative component of benzodiazepine treatment and, therefore, are not satisfied with the buspirone effect. It might also be that patients with prior benzodiazepine exposure are still having subtle withdrawal effects that are not controlled (or perhaps are even exacerbated) by buspirone treatment. In any case, this finding may provide a partial explanation for the negative outcomes with buspirone in two of the four controlled trials that appeared to have the sensitivity to demonstrate anxiolytic effectiveness. These findings should be incorporated into the buspirone SBA and the sponsor should be asked to conduct a postmarketing study to follow-up on this interesting finding.

Thomas P. Laughren 7-2-86

Thomas P. Laughren, M.D., HFN-120

cc: NDA 18-731
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Review and Evaluation of Clinical Data
Original Submission
NDA 18-731

SEP 13

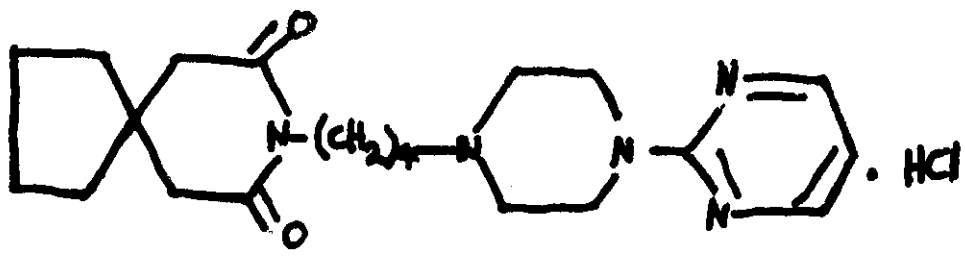
Sponsor: Bristol-Myers Company
Pharmaceutical Research & Development Division
Evansville, Indiana 47721

180 day due date: June 15, 1983

I. General Information

A. Name of Drug:

1. Generic: buspirone hydrochloride
2. Trade: Buspar
3. Chemical: 8-(4-[4-(2-pyramidinyl)-1-piperazynyl]butyl)-8-azaspiro[4,5]decane-7,9-dione hydrochloride



B. Pharmacologic Category: Anxiolytic

C. Proposed Indications: Treatment of anxiety disorders with and without accompanying depression.

D. Dosage Form and Route of Administration: 5 and 10 mg scored tablets, oral

E. Proposed Humen Dosage: 15-60 mg q.d.

II. Manufacturing Controls:

Refer to the chemistry review. To my knowledge, there are no outstanding chemistry problems which have clinical implications.

III. Pharmacology:

Below is a selected synthesis of the preclinical information. Refer to the pharmacology review for a full discussion of these data.

A. Pharmacodynamics

1. Receptor effects and neurochemistry - buspirone interacts mainly with the dopaminergic system and can be considered a mixed agonist/antagonist. Among the preclinical evidence for anti-dopaminergic activity is buspirone's antiemetic effect against apomorphine-induced vomiting in dogs and buspirone's ability to cause a dose-dependent increase in the plasma prolactin levels of male rats.

However, Buspirone does not cause catalepsy (rats, up to 10 mg/kg.) or inhibit apormorphine-induced turning in rats with unilateral 6-OH dopamine substantia nigra lesions. Activity in these tests would indicate blockade of the postsynaptic DA receptor. High doses of buspirone did cause hypoactivity. Buspirone reversed trifluoperazine-induced catalepsy in the rat.

Buspirone does effect some inhibition of DA presynaptic autoreceptors. (The antipsychotic molindone is also a DA autoreceptor antagonist). In the nigrostriatal dopaminergic system in the rat, buspirone failed to inhibit synaptosomal tyrosine hydroxylase (TH) activity (in-vitro) or γ -butyrolactone-(GBL)-induced activation of TH (in vivo) as does the autoreceptor agonist, apomorphine. Buspirone blocked the effect of apomorphine in these tests with an affinity similar to chlorpromazine. Buspirone also causes a dose-related increase of DA metabolism and TH activity in the corpus striatum, similar to that of haloperidol. There is evidence that buspirone may enhance DA neuronal activity by affecting sites in addition to the DA autoreceptor since it further increases DA cell impulse flow after a large blocking dose of haloperiodol.

The sponsor calls attention to the structural similarities between buspirone and clozapine (both heterocyclic piperazine derivatives) and piribedil (both have the pyrimidinyl-piperazine moiety).

As the sponsor states, buspirone and clozapine both inhibit rat conditioned avoidance response and apomorphine stereotypy paradigms without inducing catalepsy. Piribedil produces classical dopamine agonist activity, such as induction of stereotypy, sedation, and turning in rats with unilateral dopaminergic nigrostriatal lesions. These activities are not produced by buspirone. Buspirone, however, does produce weak turning behavior in unilaterally lesioned animals and reverses phenothiazine-induced catalepsy, both of which indicate some degree of dopamine agonism.

Buspirone does not directly react with the following receptor binding sites in vitro: alpha-1, alpha-2, and beta adrenergic, A-1 and A-2 adenosine, muscarinic, cholinergic, glutamate, glycine, H1, H2 antihistamine, Type 1 and Type 2 serotonin, and opiate. Buspirone is not a reuptake inhibitor for dopamine, norprenephrine or serotonin.

Buspirone does not affect ^{3}H-diazepam binding in acute or chronic treatment models.

Buspirone acts as a competitive inhibitor of 5HT-induced stimulation in the 5HT sensitive adenyl cyclase system (liver fluke model).

Buspirone was found to produce a dose-dependent decrease (maximum 25-30%) of ACh in rat striatum (Kolasa et al., J. Pharm. Pharmacol., 1982, 34, 314-317). The authors postulate that the effect is indirect and possibly due to buspirone's presynaptic dopamine stimulation.

2. Effects in anxiolytic drug paradigms: Buspirone blocks the conditioned avoidance response with relatively less effect on the unconditioned escape response.

   In a continuous avoidance paradigm, buspirone was effective in a dose-related fashion in causing decreased avoidances, increased number of shocks tolerated, and increased shocks not terminated.

   Buspirone (20-160 mg/kg) and diazepam (5-20 mg/kg) produced a dose-dependent anti-aggressive effect in rhesus monkeys. Buspirone caused hypoactivity only at high doses whereas effective doses of diazepam also caused hypoactivity and ataxia. Inhibition of fighting in mice which were exposed to foot shock was produced with 80-182, mg/kg of buspirone and 3 mg/kg of diazepam.

   Both diazepam and buspirone were effective in the shock-induced suppression of lever pressing by conditioned rats. Both drugs were approximately equipotent in this test.

   Both buspirone and diazepam were equipotent in inhibiting experimentally-induced conflict in cynomolgus monkeys.

3. Other actions:

   a. Seizure potentiation: Buspirone was shown to decrease the electroconvulsive threshold in the rat.

   b. Body temperature: Oral buspirone given to rats resulted in mild transient (24 hrs.) dose-related hypothermia.

   c. Effects on apomorphine: In the mice hypermotoricity paradigm, buspirone antagonized apomorphine at high doses and potentiated apomorphine at lower doses. Buspirone inhibits apomorphine-induced stereotypy in the rat. (see also receptor effects, under III.A.1).

   d. Anticholinergic activity: Buspirone lacked anticholinergic activity as measured by the protection against physostigmine lethality in the mouse and receptor studies in brain tissues. However, buspirone appears to decrease ACh levels in rat striatum (see receptor effects under, III.A.1.).

   e. Alpha-adrenergic blocking activity: Alpha-adrenergic blocking properties of buspirone were absent in several different test systems. (see also receptor effects, under III.A.1.).

   f. Abuse potential: Preclinical and human studies concerning abuse potential will be reviewed separately by Dr. Vocci of the Drug Abuse unit.

B. Pharmacokinetics

   The animal data is superseded by the human pharmacokinetic data which is now available.

C. Toxicology

1. Acute: Below is a table taken from the sponsor's submission which shows the acute toxicity of buspirone in four species. CNS toxicity (chronic convulsions, ataxia, and tremors) occurred at dose levels which were near lethal in all species.

TABLE I

Species	Sex	Dose Route	LD 50 (95% Confidence Interval) mg/kg
Rat (Adult)	Males	Oral	265 (174-404)
Rat (Adult)	Males/ Females	Oral	196 (152-252)
Rat (Newborn)	Males/ Females	Oral	415 (332-520)
Mouse	Males	Oral	655 (529-811)
Dog	Males/ Females	Oral	586 (371-925)
Monkey	Males/ Females	Oral	356 (302-420)
Rat	Males/ Females	Intraperitoneal	136 (122-152)
Mouse	Males	Intraperitoneal	164 (145-185)
Mouse	Males	Intravenous	73.3 (66.6-80.6)
Monkey	Males/ Females	Intravenous	54.3 (47.6-61.9)
Dog	Females	Intravenous Infusion	125.3 mg/kg (lowest lethal dose- infused at 80 mg/kg/hr.- 30.8 ml/hr)

2. Sub-acute: Gross or microscopic evidence of organ damage was not noted for the rat at doses of 50-200 mg/kg/day and for the monkey at doses of 37.5-150 mg/kg/day. These were oral administration studies of 3 months duration. See the pharmacologist's review for a discussion of the various toxic effects.

3. Chronic: Buspirone was orally administered to rats over 12 months in doses of 48 mg/kg/day, 80 mg/kg/day, and 160 mg/kg/day. Dose-related CNS effects and tachycardia occurred. Also, dose-related pulmonary histiocytosis occurred.

   The monkey was given oral doses of buspirone of 25 mg/kg/day, 50 mg/kg/day, and 100 mg/kg/day for 12 months duration. There were increases in liver, kidney, adrenal, and heart weights and decreases in testicular weights, but there were no gross or microscopic pathologic findings. Several monkeys died, mainly during the first two months of the study, and exhibited pathologic evidence of gastroenteritis. This was thought to be due to a gastric infection common in the species.

4. Carcinogenicity studies: The sponsor concluded that buspirone was not a tumorigen in the rat given doses of 48-160 mg/kg/day for 20 months or in the mouse given doses of 50-200 mg/kg/day for 78 weeks.

5. Reproduction and Teratology: The sponsor concluded that buspirone does not alter the reproduction of the male or female rat, does not produce skeletal or visceral abnormalities in rats or rabbits, or produce any adverse effect on fetal development, birth weight or post-natal growth or survival; all at doses of 36 mg/kg given at a time appropriate for each test.

6. Mutagenicity: The Salmonella typhimurium incorporation tests, with and without enzymatic conversion, were negative.

IV. Clinical Background

A. Brief history of the drug and identification of important issues

Buspirone was synthesized in 1968 by Mead-Johnson and was intended for investigation as an antipsychotic agent. IND [redacted] for buspirone was submitted in 1972. In some of the first clinical studies of buspirone, doses up to 2400 mg were used. Although fairly well tolerated, buspirone did not produce antipsychotic activity except very transiently. Upon exploring buspirone's activity further in preclinical tests, Mead-Johnson concluded that buspirone showed promise as an anxiolytic. After initial dose finding and double-blind studies with psychoneurotic outpatients, buspirone was tested in this patient population in a major drug development program.

In addition to buspirone's clinical efficacy as an anxiolytic, there are several additional issues raised in this NDA by the sponsor. The sponsor cites unique properties for buspirone which are as follows:

1. that buspirone is an effective anxiolytic even in the face of accompanying depression,

2. that buspirone does not produce more sedation than placebo,

3. that buspirone does not decrease mental alertness and therefore no warning is needed for its use while performing tasks which require mental alertness,

4. that buspirone has no abuse potential.

One issue that I am identifying as the reviewer is that of buspirone's relative safety to other anxiolytic agents. Buspirone was originally developed as an antipsychotic agent, and shares some common features with such drugs. Buspirone is a mixed dopamine agonist/antagonist, (see III.A.1. above) and its antagonist properties in doses used for anxiolytic efficacy need to be carefully examined. The major concern is whether buspirone blocks dopaminergic receptors in therapeutic anxiolytic doses to such an extent that it would have a potential for producing tardive dyskinesia. Such a potential would reflect unfavorably on buspirone's safety relative to currently marketed treatments for anxiety, even though buspirone may have other more favorable features. Any other similarities of buspirone to neuroleptics with respect to side effect profile, will be carefully examined and discussed. An example of such an effect would be extrapyramidal reactions.

The parent drug is immediately metabolized and very short-lived in plasma. One might speculate that the parent drug is responsible for buspirone's DA receptor blocking properties and brief antipsychotic activity in large doses. The active metabolite(s) responsible for the anxiolytic action may not possess DA blocking activity. Such a view is still very hypothetical and would need to be confirmed.

V. Literature Review

The sponsor includes a narrative summary of 31 published and unpublished papers. In addition, a copy of the proceedings from a symposium "Buspirone: A Clinical Review of a New Non-Benzodiazepine Anxiolytic" which was published in the Journal of Clinical Psychiatry, Vol. 43: 12 [SEC. 2] 1-116, 1982. The 31 papers appear to be published and unpublished reports of studies which were performed under the sponsorship of Bristol-Myers and are included and described elsewhere in this NDA. Likewise, the symposia proceedings, published in the December 1982 issue of the Journal of Clinical Psychiatry represent a Mead Johnson sponsored conference which included material that is discussed elsewhere in the submission.

Pertinent material from the literature submitted will be considered and included in the appropriate sections of the NDA review.

VI. Foreign Data

The firm includes foreign data in the Safety section of this NDA submission, but includes no foreign data in the Efficacy section. The foreign safety data will be discussed in the overall review of safety below. The firm will be contacted to ascertain whether if there is any foreign efficacy data.

VII. Clinical Studies

Table II, obtained from the sponsor's summary, outlines the buspirone clinical program. In the discussion below, the well controlled efficacy and safety trials will be emphasized.

A. Biopharmaceutical Studies

The ADME studies will be discussed in detail in the review by Biopharmaceutics. Only study 1140 will be reviewed here. Following a single oral dose of 20 mg of C^{14} labeled buspirone to four healthy male volunteers, 29-63% of buspirone was excreted into urine and 28-38% was excreted into feces. The parent compound was only 1% of radioactivity in plasma samples drawn intermittently throughout 24 hrs. following drug administration. The elimination half-life for plasma radioactivity was approximately 5 hours, with no radioactivity detected in the plasma by 24 hrs. The sponsor states that in humans, buspirone is metabolized by hydroxylation and oxidative cleavage.

B. Clinical Pharmacology

1. Tolerance - single dose - Study # 111

   a. Investigator/Location:

   b. Rationale/Design: This was a single-blind, placebo controlled study designed to determine the oral single dose tolerance range of buspirone in 9 male volunteers. Single rising doses from 25 mg to a tolerated level were administered to each subject. The sponsor reports the following: the side effects most commonly noted included myosis, nausea or vomiting, dizziness, drowsiness, and gastric distress. Other side effects reported

TABLE II

BUSPIRONE CLINICAL PROGRAM

Study Type	Investigator	Study No.	No. Pts. / Subjects* Total	Buspirone
Clinical Pharmacology				
Tolerance - Single-dose		111	9	9
Tolerance - Multiple-dose		163	21	18
Tolerance - Antipsychotic activity		246	10	10
Antianxiety - Dose-range		657	30	30
Sleep study		684	9	9
		Subtotal	79	76
ADME**				
Metabolism and Pharmacokinetics				
Assay Development		599	7	7
Radiolabeled Drug Disposition		1067	4	4
Radiolabeled Drug Disposition		1130	4	4
Pilot Bioavailability		1140	4	4
Bioavailability		1201	6	6
Dose Proportionality		1281	24	24
Assay Validation / Metabolite Isolation		1292	28	28
Bioequivalence - Capsule / Tablet		1349	4	4
Bioavailability / Food		1379	24	24
		1439	6	6
		Subtotal	111	111
Well-Controlled Efficacy and Safety***				
B v D v P		784	60	20
B v D v P		964	240	81
B v D v P		965	190	64
B v D v P		966	120	40
B v D v P		1012	129	43
B v D		1000	140	105
B v D		1048	66	51
B v D		1049	118	89
B v C		1029	139	106
B v C		1032	66	50
B v C		1041	131	99
		Subtotal	1399	748
Special Studies				
Functional Impairment		1003	30	30
Functional Impairment		1207	48	16
Functional Impairment		1290	24	24
Functional Impairment		427	12	12
Functional Impairment		328	12	12
Functional Impairment		470	8	8
Neuroendocrine		1324	9	9
Neuroendocrine		529	10	10
Abuse Potential		1367	36	36
Abuse Potential		1380	12	12
		Subtotal	201	169
		Grand Total	1790	1104

*No. of patients or subjects entered in the study, and included in safety analysis.
**ADME = Absorption, Distribution, Metabolism, and Excretion
***B = buspirone, D = diazepam, C = clorazepate, and P = placebo

D. Antianxiety - Dose Range - Study # 657

1. Investigator/Location:

2. Rationale/Design: This was a 4-week open clinical trial in 30 psychoneurotic outpatients who were administered from 30-105 mg/day of buspirone.

3. Results/Conclusions: Half of the patients reported adverse experiences including sedation, nausea and vomiting, restlessness, blurred vision, confusion, feeling "spacy" and others. There were no clinically significant changes in laboratory, EKG, or other toxicity monitoring reported. The sponsor concluded that buspirone was well tolerated in the dosages used and showed some promise in its effectiveness as an anxiolytic.

E. Sleep Study - Study # 684

1. Investigator/Location:

2. Design/Rationale: This was a double-blind, randomized, cross-over trial comparing 3 dosages (25 mg buspirone, 50 mg buspirone, and placebo) in 9 mildly insomniac male participants. EEG and electrooculogram were used to monitor the patients in a sleep laboratory setting.

3. Results/Conclusions: Buspirone was not effective as a hypnotic at the dosages used in this study.

F. Controlled Efficacy and Safety Trials

1. Placebo Controlled Trials

There were five placebo controlled studies performed according to similar protocols, three by separate investigators and two by the same investigator.

Each of these investigations was a double-blind, randomized, parallel, placebo and diazepam controlled trial of buspirone in adult psychoneurotic outpatients who had a DSM II diagnosis of depression with or without accompanying significant depression. After these studies were completed, the sponsor cross-referenced symptoms from the entry criteria (which were recorded on the patient report forms) to the current DSM III criteria for Generalized Anxiety Disorder to show that these subjects fulfilled the newer criteria as well.

Each study was 4 weeks in duration with evaluations at baseline and weekly thereafter. All of these studies except # 764 specified continued treatment following the initial 4 week double-blind phase. The continuation of treatment was done on a double-blind basis.

Subjects were males and females from 18-60 years who had a history of anxiety for at least one month and a score of at least 20 on the Hamilton Anxiety Rating Scale (HAM-A). Subjects with a history of psychosis were excluded. Subjects who scored higher on the Raskin Depression Scale than the Covi Anxiety Scale were excluded except for study # 764. Patients who had significant renal, liver, or cardiovascular disease as those who were addicted to drugs or alcohol were not allowed into the study. Subjects must not have received any psychotropic agent within 7 days prior to study participation.

Dosages of buspirone and diazepam were from 15-60 mg in study # 764 and 10-50 mg for the other studies.

Evaluation criteria included the HAM-A, Physician Questionnaire, Hamilton Depression Scale (HAM-D), Symptom Checklist, (SCL), Profile of Mood States (POMS), Sleep Evaluation, Doctor's Disposition and Raskin Covi Scales.

Analyses for all outcome variables were performed for the overall efficacy population and for a subpopulation of subjects designated as "high depression." Participants who had a HAM-D total score of 18 were included in this high depression subpopulation.

Baseline evaluation and safety assessments included the medical and psychiatric history, physical examination, vital sign monitoring, hematology and clinical laboratory, urinalysis, and EKG. Further details of the safety evaluation conducted will be discussed in the separate safety section below.

All subjects were included in the safety analyses. Subjects were excluded from efficacy analyses for the following reasons:

(a.) participation in study for less than 7 days,
(b.) no HAM-A for week 1 or week 2 or
(c.) use of another investigational drug, an antidepressant, or a neuroleptic agent during the treatment period.

Exclusions will be discussed separately for each study. See Table III below, taken from the sponsor's submission, for the numbers of patients enrolled in each study and the number subsequently included in the efficacy analyses.

TABLE III

Numbers of Patients in Bv. D. v.P Studies

Investigator	Study No.	No. Patients Entered			No. Patients Efficacy		
		B	D	P	B	D	P
	764	20	20	20	18	18	18
	994	81	81	78	68	71	73
	995	64	62	64	57	50	56
	996	40	40	40	29	32	29
	1012	43	43	43	40	39	38

a.

(2) Description of Patients: 60 patients were randomized into the study. Two patients from each treatment group were excluded from the efficacy analysis, leaving 18 in each group who are included in the efficacy calculations. Two subjects in the buspirone group were excluded due to "lost to follow up" and drug administration of less then 7 days. Two of the diazepam subjects were excluded due to drug administration of less than 7 days. Two placebo subjects were excluded, one due to drug administration of less then 7 days and another due to no HAM-A rating at week 1 or 2 and subsequent patient-initiated discontinuation from the trial.

Nine (50%) of buspirone, 8 (44%) of the diazepam, and 9 (50%) of the placebo patients had a baseline HAM-D score of at least 18.

In the buspirone group there were 4 subjects with concomitant medications: 2 with Premarin, 1 with Aldoril (for hypertension) and 1 with Ovulen. In the diazepam group there were 3 patients with concomitant medication: 1 with Enovid-E, 1, 1 with penicillin (for a tooth infection), and 1 with Premarin. In the placebo group there were 4 patients with concomitant medications: 1 each with Demulen, Ambenyl (expectorant), Demulen, and Aldoclor (for hypertension).

The mean maximum daily dose of drug for subjects in each treatment group is shown in Appendix 1. Sixty-seven percent of the subjects in the buspirone and diazepam group participated for the full 4 weeks. Fifty-six percent (10) of the placebo group were in the study for the 4 weeks.

(3) Outcome: (a) HAM-A and HAM-D: see tables in Appendices II and III for HAM-A and HAM-D total score (actual) results. For subjects who dropped out before completion of the trial, the last available score is carried forward for each week's calculation. The results reported in this review are baseline to endpoint (using the last score carried forward as just described) calculations. Although the HAM-A and HAM-D scores in Appendices II and III are actual mean total scores, the significant results reported in this review are based upon the sponsor's calculations of adjusted mean scores. Results reported here as significant are at least at the p = .05 level in a two-tailed test.

In study # 764, Buspirone was better than placebo at least the p = .05 level for HAM-A total and for 13 items on the HAM-A.

The high depression subpopulation showed a significant difference according to the HAM-A on both the total score and 11 items on the HAM-A when compared to placebo.

The buspirone group was significantly more improved than placebo on the HAM-D total and 10 of 21 HAM-D items, including item 1 which is Depressed Mood. The high depression subpopulation was significantly better for buspirone than placebo at endpoint on the total HAM-D score and 8 of 21 HAM-D items. See Appendix III for a comparison of the HAM-D scores among the different treatment groups.

Diazepam was significantly better than placebo for the HAM-A total and 6 of the HAM-A items. Unlike buspirone, diazepam was not better than placebo on the depressed mood item of the HAM-A. For the high depression subpopulation, diazepam was better than placebo on the HAM-A total and 3 of the HAM-A items (Tension #2, Fears #3, and an Autonomic Symptoms #13).

For the HAM-D total score, diazepam was significantly better than placebo. In the group which included all patients, diazepam was better than placebo on 3 items of the HAM-D (Suicide #3, Hypochondriasis #15, and Insomnia, early #4). For the high depression subpopulation, diazepam was significantly better than placebo on the total HAM-D score and on 4 HAM-D items (Suicide #3, Insomnia, Early #4, Somatic General #13 and Obsessional and Compulsive Symptoms, #21).

(b) Physician's Questionnaire

For all three of the Physician's Questionnaire items (Global Psychopathology, Doctor's Opinion of Subject's Change, and Subject's Opinion of Subject's Change), both the buspirone and diazepam groups showed a significantly greater percentage of patients with improvement than the placebo group for all efficacy patients at endpoint. The results were similar for the subpopulation with HAM-D total scores greater than 18 except for the global psychopathology item which was not significantly different among the treatment groups.

(c) The Doctor's Disposition scale items will not be discussed in detail since it is not a major outcome variable. However, the results were consistent with the major scales showing better results for buspirone and diazepam than placebo.

(d) Sleep Evaluation

This was a complex questionnaire and again, is not a major outcome variable. However, both diazepam and buspirone patients were rated as signficantly more rested than placebo patients at endpoint.

(f) Symptom Checklist (SCL)

Subjects on buspirone and diazepam were significantly better than placebo on the SCL total score and all factors (Anxiety, Cognition, Depression, Interpersonal Sensitivity, Somatization, Fearfulness, Inferiority and Tension. The high depression subpopulation had similar results.

(g) Profile of Mood States (POMS)

Subjects on buspirone and diazepam did significantly better than those on placebo according to the overall efficacy analysis for total score and several factor scores including Confusion, Depression/Dejection, Fatigue and Tension/Anxiety. Results were similar for the high depression subpopulation.

(4) Side Effects

(a) General

Three (15%) of the buspirone patients, 10 (50%) of the diazepam patients and 7 (35%) of the placebo patients experienced adverse effects. One of the buspirone patients experienced weakness, dizziness, and light-headed feeling: this effect was mild and no action was taken. Another buspirone patient experienced dizziness, light-headedness and the dose was reduced. A third buspirone subject experienced weakness, dizziness, light-headed feeling, and cold sweat and the subject was discontinued from the trial. All three subjects are included in the efficacy analysis.

(b) Clinical laboratory and hematology

None of the values outside of the normal range were considered to be clinically significant for any of the treatment groups. Upon scanning the data, I agreed with the conclusion.

(c) Physical Examination - physical exams were conducted within one week prior to study participation and within one week subsequent to study participation. There were no physical abnormalities reported at endpoint that had not been reported at baseline for any buspirone patient.

(d) EKGs - the investigator was not required to perform EKGs for subjects during the study.

(e) Vital Signs - systolic and diastolic blood pressure, pulse, and weight were measured pre- and post treatment. Apparently no measures of supine and standing blood pressures were taken to determine whether orthostatic hypotension occurred. The sponsor indicated that patients had blood pressure variations greater than 15 mm of Hg or pulse variations greater than 10 beats per minute. None of them were considered to have changes that were clinically significant. My perusal of this data leads me to the same conclusion.

(5) Evaluation and Comments

This study strongly supports the efficacy of buspirone as compared to placebo in the treatment of this study population. In general, buspirone was comparable to diazepam in efficacy. For the HAM A and HAM-D depression items, buspirone was also signficantly better than placebo while diazepam was not. Diazepam as well as buspirone, was significantly better than placebo on the depression related factors included in the POMS and SCL-56.

b. Study #994

(1) Investigator/Location:

a. The patients were seen in a private outpatient practice. There were seventeen coinvestigators.

(2) Description of Patients: 210 patients were randomized into the study. 212 subjects (68 buspirone, 71 diazepam and 73 placebo) were included in the efficacy analysis. 13 buspirone, 10 diazepam, and 5 placebo subjects were excluded from the efficacy analysis. Of the 13 buspirone subjects, 9 were excluded because of drug duration of less than 7 days, one subject had no HAM A for week 1 or week 2, one subject was off drug for seven days during the study, one subject had concomitant use of Atarax and one subject was assigned a duplicate number. Of the 10 diazepam patients, 5 had drug duration for less than seven days, 3 had no HAM-A week 1 or week 2, and 2 subjects had duplicate numbers. For the placebo exclusions, 4 had drug duration of less than seven days and one had no HAM-A for week 1 or week 2. It appears that one of the investigators in the study (Dr. Brown) entered one patient three times into the study and another patient two times into the study. The sponsor recognized this error and only included these subjects' first participation in the analysis.

Thirteen of the buspirone patients, 17 diazepam patients and 18 placebo patients included in the efficacy analysis had received concomitant medications. Most of the concomitant medications were taken by the study subjects prior to study entry. Only two buspirone patients and one placebo patient received medication during the study that they had not been receiving at the entry of the study. Although there are some concomitant medications which may have had an effect on the symptoms measured during the study (e.g., Inderal, Sy oid), the numbers taking such medication seems small and randomly distributed among the three treatment groups.

The mean maximum daily dose of subjects in each treatment gro shown in Appendix I.

Sixty-eight percent of the subjects in the buspirone group, 72% of the subjects in the diazepam group, and 48% of the subjects in the placebo group were in the study for the full 4 weeks.

(3) Outcome: See Table in Appendix II. In the HAM-A total, buspirone and diazepam were better than placebo at least the $p = .05$ level. Both the buspirone and diazepam groups were significantly more improved on 11 of the 14 items on the HAM A. Thirty-two (47%) of buspirone, 34 (48%) of the diazepam and 43 (59%) of the placebo patients had a baseline HAM D score of at least 18. For the high depression subpopulation, both buspirone and diazepam were better on HAM A total score, the Psychic and Somatic Factors, and several of the HAM A items. Buspirone was better than placebo on 3 HAM A items, and diazepam was better than placebo on 4 HAM A items in this high depression subpopulation.

For the HAM-D total score, both buspirone and diazepam were better than placebo. The buspirone group was significantly more improved than placebo on 10 of the 21 HAM-D items, and the diazepam group was significantly more improved than placebo on 8 of the items. See Appendix III for comparison of the HAM-D scores among the different treatment groups.

For the high depression subpopulation, both buspirone and diazepam groups were significantly more improved than the placebo on total score and for several of the items.

(b) Physician's Questionnaire

For all three of the Physician's Questionnaire items (Global, Psychopathology, Doctor's Opinion of Subject's Change, and Subject's Opinion of Subject's Change), both the buspirone and diazepam groups showed a significantly greater percentage of patients with improvement than the placebo group for all efficacy patients at endpoint. The results were similar for the subpopulation with HAM-D scores greater than 18. Overall, the high depression subpopulation began the study with a higher Global Psychopathology Assessment than for the entire efficacy patient population.

(c) The Doctor's Disposition Scale

The Doctor's Disposition Scale items will not be discussed in detail since it is not a major outcome variable, however, the results were consistent with the major scales showing better results with buspirone and diazepam than placebo.

(d) Sleep Evaluation

Both diazepam and buspirone patients were rated as significantly more rested than placebo patients at endpoint. This is a complex questionnaire and is not a major outcome variable. Therefore, results will not be discussed in detail.

(f) Symptom Checklist

At endpoint, buspirone patients were significantly more improved than placebo subjects for the following: Total Score, Anxiety Factor, Fearfulness Factor, Interpersonal Sensitivity Factor. Diazepam subjects were significantly more improved than placebo on the following: Anxiety Factor, Fearfulness Factor: and more improved than both the buspirone and placebo groups on the Somatization Factor. For the high depression subpopulation, there were no signficant differences between treatment groups (except for superiority of buspirone over diazepam on the Inferiority Factor).

(g) Profile of Mood States

Subjects on buspirone and diazepam did signficantly better than those on placebo according to the total score. Buspirone was signficantly more improved than placebo on the Anger/Hostility, Confusion, Fatigue, and Tension/Anxiety Factors. Diazepam patients were significantly more improved than placebo on the Tension/Anxiety and Vigor Factors. For the high depression population, the buspirone group was signficantly more improved than the other two groups on the Fatigue Factor. Buspirone was also more significantly improved than diazepam alone on the Anger/Hostility Factor.

(h) Raskin-Covi Scale

Subjects on buspirone and diazepam were significantly more improved than the placebo group in both the Raskin Depression Scale and the Covi Anxiety Scale total scores. For the high depression subpopulation, both buspirone diazepam groups did significantly better than placebo on the Covi Anxiety Scale but not on the Raskin Depression Scale.

(4) Side Effects

(a) General

Forty (49%) of the buspirone patients, 51 (63%) of the diazepam patients and 12 (15%) of the placebo patients experienced adverse effects.

Eighteen (22%) of the buspirone patients, 26 (22%) of the diazepam patients and 9 (12%) of the placebo patients experienced drowsiness.

Twenty-four (30%) of buspirone patients, 35 (43%) of the diazepam patients and 4 (5%) of the placebo patients had their dosage reduced, suspended or discontinued due to adverse events.

Only one subject (#299) on buspirone had the side effect of "rigid/stiff muscles." There was also one occurrence (#374) in the buspirone group of involuntary movement as a side effect which was thought to be related to the test drug. There is one occurrence in the buspirone group of tremor.

(b) Clinical Laboratory and Hematology

None of the values outside of the normal range were considered to be clinically significant for any of the treatment groups. Upon scanning the data, I tend to agree with this conclusion. However, this data will be further reviewed in the overall safety section below.

(c) Physical Examination

Physical exams were conducted within one week prior and within one week subsequent to patient participation. Four subjects in the buspirone group were considered to have changes on physical exam record. One buspirone had a macular pacular rash, another had repeated angina (not considered by the investigator to be an adverse reaction), a third had urinary frequency, and another stomach discomfort.

(d) EKGs

EKGs were performed pre- and post study. The sponsor's table shows four post-study abnormalities for buspirone. One subject had a sinus arrhythmia (bradycardia). Another subject had first degree heart-block. Two other patients are reported who had sinus rhythm and "normal limits for age" reported. There were two abnormalities reported for diazepam and three for placebo.

Buspirone patient # 166 who had a bradycardia, had this abnormality at baseline and had no significant EKG change during the study. Subject #300 on buspirone also had his first degree heart-block throughout the study with no change in his EKG. The other two subjects, #478 and #486 also had no significant EKG changes during the study period.

Likewise, the subjects who had abnormal EKG tracings at the conclusion of the study for the other treatment groups, had shown no significant change in their EKGs from baseline to endpoint.

(e) Vital signs

It was not until 5 months after the initiation of the study that the protocol was amended to provide for pulse and blood pressure to be repeated each weekly visit. Using the available data, the sponsor indicated the patients who had blood pressure variations greater than 15 mm of mercury or pulse variations greater than 10 beats per minute. None of them were considered to have changes that were clinically significant. My perusal of the data leads me to the same conclusion. Apparently no measures of supine and standing blood pressures were taken to determine whether orthostatic hypotension occurred.

(5) Evaluation and Comments

This study also supports the efficacy of buspirone as compared to placebo in the treatment of the study population. In general buspirone was comparable to diazepam in efficacy.

c. Study # 995

(1) Investigator/Location:

The setting is described as a private, research oriented outpatient practice. There were seventeen additional investigators.

(2) Description of Patients: 190 patients were randomized into the study. Fifty-seven buspirone, 50 diazepam and 56 placebo subjects were included in the efficacy analysis. In the buspirone group, there were 3 patients excluded because of receiving the study drug for less than 7 days: One subject was over 65 years (out of age limits as stipulated in the protocol); One subject received medication within 7 days prior to the study; Two patients were excluded who had a washout of less than 4 days. In the diazepam group 5 subjects were excluded because of drug duration of less than 7 days: 5 subjects were excluded because of age over 65; Two subjects were excluded because they were entered into the study twice due to an investigator error. In the placebo group there were 7 subjects who were excluded for drug duration of less than 7 days: One subject was excluded because there was no HAM A for week 1 and week 2.

Thirty-nine (68%) of the buspirone, 35 (70%) of the diazepam and 33 (59%) of the placebo patients were included in the high depression subpopulation.

Fourteen (20%) of the buspirone, 18 (36%) of the diazepam and 14 (25%) of the placebo efficacy patients received concomitant medication during the 4 week study. Only 3 of the buspirone, 7 of the diazepam and 2 of the placebo patients began the concomitant medication after the start of the double-blind period. Although there are some medications which would be expected to have an effect on the target symptoms in the study (e.g. Inderal, Synthroid), these instances are not numerous and randomly distributed among the treatment groups.

Thirty-seven (65%) of the buspirone group, 40 (80%) of the diazepam group and 41 (73%) of the placebo group participated for the full 4 weeks.

(3) Outcome:

(a) HAM-A and HAM-D

See Appendices II and III for HAM-A and HAM-D total scores (actual) by week. For the HAM A, the buspirone group was significantly more improved than the placebo group on total score and the Somatic Factor, in the overall analysis from baseline to endpoint.

Diazepam was significantly better than placebo from baseline to endpoint on the Psychic Factor, with trends favoring the diazepam group for total score and the Somatic Factor. The active treatment groups did not differ significantly from each other on the HAM-A variables. Buspirone was better than placebo on three HAM-A items: # 5, Intellectual, # 8, Somatic Sensory, and # 13 Autonomic. Diazepam was better than placebo on 3 HAM-A items: # 1, Anxious Mood, # 14 Behavior, and # 13 Autonomic.

For the high depression subpopulation, both buspirone and diazepam groups were significantly more improved than the placebo group for total score in both psychic and somatic factors from baseline to endpoint on the HAM-A. Buspirone was better than placebo on four HAM A items: # 5 intellectural, # 14 behavior, # 11 gastro intestinal, and # 13 Autonomic. Diazepam was better than placebo on one item # 14 behavior.

For HAM-D total scores from baseline to endpoint both buspirone and diazepam males were significantly more improved than placebo males. Males were also more improved in the buspirone and diazepam group than placebo for the Anxiety/Somatization Factor of the HAM-D. The two active treatment groups did not differ from each other. The only item that was significantly different among the three treatment groups at endpoint was # 3 (suicide), on which buspirone was better than placebo. For the high depression subpopulation, the buspirone group was significantly more improved than the placebo group on the Retardation Factor. There were no other significant differences. For HAM-D items, buspirone was better than placebo for the item # 11 anxiety, somatic and item # 3 suicide. Diazepam was better than placebo on item # 11 anxiety, somatic.

(b) Physician's Questionnaire

There is no significant treatment differences on any of the three Physician's Questionnaire questions with the overall efficacy population from baseline to endpoint. At endpoint, 56 percent of the buspirone, 62 percent of the diazepam and 54 percent of the placebo group was judged to be either not ill, or very mild, or mild for the global psychopathology question. For Doctor's Opinion of Subject Change, 58 percent of the buspirone, 66 percent of the diazepam and 48 percent of the placebo groups were rated as either very much better or much better. For the Subject's Opinion of Subject's Change, 56 percent of the buspirone group, 62 percent of the diazepam group and 45 percent of the placebo group were rated as very much better or much better. For the high depression subpopulation, there were also no significant differences among the three treatment groups from baseline to endpoint.

(c) Doctor's Disposition:

Response for both buspirone and diazepam groups was significantly better than placebo for the question that asked whether the subject would want to stay on the same medication. There were no other significant differences for buspirone. For diazepam, there were significant comparisons versus placebo for the Subject's Evaluation of Improvement, the Physician's Evaluation of Improvement, and the comparison to the last psychiatric drug taken.

For the high depression subgroup, buspirone was better than placebo at endpoint, for the question that asked the subject whether he or she would want to stay on the same medication. There was a trend favoring buspirone on the Subject's Evaluation of Improvement and Physician's Evaluation of Improvement. Diazepam was better than placebo on the question asking whether the subject would want to stay on the same medication, on the comparison to the last psychiatric drug taken, for the subject evaluation of improvement and the physician's evaluation of improvement.

(d) Sleep Evaluation:

The only significant comparison to placebo from baseline to endpoint was of the diazepam group where the frequency of awakening was lessened. For the high depression subgroup, both buspirone and diazepam groups showed significant differences (or trend toward) greater improvement than the placebo group on the how long to fall asleep, how often awakened, and the how well rested questions.

(e) Symptom Check List:

For the overall baseline to endpoint analysis, buspirone was significantly favored over placebo for the total score, Anxiety factor, Cognition factor, Depression factor, Fearfulness factor, Somatization factor, with trends favoring buspirone for the Inferiority and Interpersonal Sensitivity factors. The diazepam group was favored over placebo only for the Inferiority factor, but was favored for the male population over placebo for the total score and several other factors.

For the high depression subpopulation, the baseline to endpoint analysis showed the buspirone groupto be signficantly more improved than the placebo group on the total score and all factors.

The diazepam group was more improved than placebo on total score, Anxiety factor, Fearfulness factor, Interiority factor, Interpersonal Sensitivity factor, Somatization factor, and Tension factor with a trend for the Depression factor.

(f) Profile of Mood States

From baseline to endpoint, the buspirone group was significantly more improved than placebo on total score and the following factors: Confusion, Fatigue, Tension/Anxiety and Vigor. Diazepam was better than placebo for the following factors: Anger/Hostility, Depression/Dejection, with a trend toward diazepam for the Tension/Anxiety factor.

For the high depression subpopulation, buspirone was better than placebo from baseline to endpoint for the total score and for all factors. For the diazepam, placebo comparisons, diazepam was better on the total score and the following factors: Anger/Hostility, Confusion, Tension/Anxiety, with trends for the Vigor and Fatigue factors. It is noted that for the high depression subpopulation buspirone was better than placebo on the Depression/Dejection factor whereas diazepam was not. Busperone was also better for the subpopulation on items such as unhappy, hopeless, discouraged, and guilty. Both the diazepam and buspirone tended to be favored for items having to do with tension such as tense, uneasy, restless, and nervous.

(g) Raskin-Covi Scale

Both the buspirone and diazepam groups were significantly more improved than the placebo on the Covi-Anxiety Scale total score. Buspirone and diazepam groups were also significantly more improved than placebo for the Raskin-Depression Scale. The buspirone group was signficantly more improved than the placebo for the Behavior item on the Raskin-Scale and the Verbal Report and Somatic Complaint items on the Covi-Anxiety Scale. The diazepam group was more improved than placebo on the Verbal Report item of the Covi.

For the high depression subpopulation, the buspirone and the diazepam groups were better than placebo for the Covi-Anxiety scale total score.

Neither buspirone nor diazepam was better than placebo for the baseline to endpoint total Raskin-Depression scale score. The buspirone was significantly better than the placebo group on the Verbal Report and Behavior items of the Raskin and all three Covi items. The diazepam group was significantly better than placebo on two Covi items: Verbal Report, and Behavior.

(4) Side Effects

(a) General:

10 (6%) of the buspirone, 22 (36%) of the diazepam and 11 (17%) of the placebo patients experienced adverse effects during this four week study. The numbers of subjects experiencing adverse effects resulting in dosage reduction or discontinuation are as follows: buspirone, six (9%), diazepam 13 (21%): and placebo, 7 (11%). Three of the buspirone subjects, 15 of the diazepam subjects and 1 of the placebo subjects reported sedation. It is noted that there were two patients with chest pain of unknown relation to test drug. The side effects will be further discussed in the overall safety analysis below.

(b) Laboratory:

None of the abnormalities which occurred were considered to be clinically significant. It is noted that subject #644 had an elevated LDH measured at day 30. SGOT and SGPT were normal throughout the study period. On perusing the data, I tend to agree with the sponsor's conclusion.

(c) Physical examination:

None of the changes in the physical examination are considered to be of clinical significance. Only one reaction, that of patient No. 682 who experienced "myospasm," appears to be of significance.

(d) EKG:

There were five abnormal EKGs on buspirone, five on diazepam, and 11 on placebo. Two subjects on buspirone had abnormalities at baseline with no follow-up. Two subjects had abnormal EKGs at baseline with no significant change during the study. One subject on buspirone had an abnormal EKG at baseline (non-specific QRS is widening) and ST depression and T-wave blunting at endpoint.

(e) Vital signs: The sponsor states that there were no clinically significant changes in pulse or blood pressure. For several patients (Number 323; Number 452, Number 457, Number 465 and possibly others) on buspirone there appears to be a lowering of blood pessure, athough the values were still within the normal range. Two subjects (Number 323, Number 459) on buspirone had heart rates below 60.

(5) Evaluation/comments:

This study is supportive of the efficacy of buspirone as compared to placebo in the treatment of Generalized Anxiety Disorder. It is not as strong as the studies 764 and 994. The differences between the results of the placebo group and for the buspirone group is not as large as in the two previous studies. It is noted that buspirone had a higher drop-out rate than diazepam or placebo in this study. Sixty-five percent of the buspirone patients as compared to 80 percent of the diazepam and 73 percent of the placebo patients remained in the study for 4 weeks. Forty-seven percent of the placebo group as compared to 52 to 53 percent of the active treatment groups had at least a fifty precent decrease on the handmade total scored endpoint. There are, a number of variables which do favor both active treatment groups.

d. Study # 996

(1) Investigator/location:

Principal Investigator:

The setting was described as a private, research oriented, outpatient practice.

(2) Description of patients: 120 patients were randomized into the study: 40 subjects each in the buspirone, diazepam and placebo groups. 90 subjects were included in the efficacy analysis (29 buspirone, 32 diazepam and 29 placebo). 14 of 29 (48%) of the buspirone patients, 21 of 32 (66 %) of the diazepam patients and 18 of 29 (62%) of the subjects included in the efficacy analysis remained in the study for 4 weeks.

19 (66%) of the buspirone, 26 (81%) of the diazepam and 20 (74%) of the placebo efficacy patients received concomitant medications. Five of the buspirone, 13 of the diazepam and 11 of the placebo began concomitant medication after the start of the double-line period. The types of concomitant medications appear to be randomly distributed and therefore probably had no effect on the study of common period. There were exclusions in each treatment group for concomitant use of psychoactive medication.

All of the buspirone, 94 percent of the diazepam and all of the placebo subjects had the same interviewer endpoint as they had at baseline.

(3) Outcome:

(a) Ham-A and Ham-D

See Appendices II and III for the Ham-A and the Ham-D total scores (actual) for all efficay patients and the high depression subgroup at baseline and at each week during the study.

For the Ham-A total score from baseline to endpoint for all patients included in the efficacy analysis and for all male efficacy patients there were no significant treatment differences. Diazepam was significantly better than placebo for the Psychic factor of the Ham A for female patients. Diazepam was better than buspirone for the total score and the Psychic factor of the Ham A for female patients only. Diazepam was significantly better than placebo for the analysis which included all efficacy patients for the following items: # 1 - anxious mood, #4 - insomnia and #14 - behavior. Diazepam was better than buspirone for item # 4 - insomnia. Buspirone was not significantly better than placebo for any of the Ham-A items.

Sixteen (55 %), fifteen (47%) and thirteen (45%) of the buspirone, diazepam, and placebo efficacy patients were included in the high depression subpopulation. For the Ham-A there was no significant differences among the three treatment groups for high depression subjects on total score. For Ham-A items, the diazepam group was significantly better than placebo for item no. 4 insomnia for the high depression subjects. There were no other significant differences among the three treatment groups for the high depression subpopulation on Ham-A.

For the Ham-D total from baseline to endpoint total there are no significant differences among overall treatment groups. For Ham-D factors, diazepam was better than placebo for the Anxiety/Somatization Factor, Cognitive Disturbance Factor,

and diazepam was better than buspirone for these two factors, Sleep Disturbance, and Retardation Factor (trend). For Ham D items at endpoint, diazepam was better than placebo for item #4 insomnia, early and diazepam was better than buspirone for #4 insomnia, early #5 insomnia, middle and #10 anxiety, psychic.

For the high depression subpopulation the diazepam was better than placebo on the sleep disturbance factor (trend), placebo was better than diazepam on the Retardation Factor (trend). Busperone was better than diazepam for the Retardation Factor, and diazepam was better than buspirone for the Sleep Disturbance Factor. For items in this high depression subpopulation, the diazepam group had a greater reduction from baseline than did the buspirone group for #5 insomnia, middle.

(b) Physician's Questionnaire:

From baseline to endpoint, there were no significant differences among the three treatment groups on any Physician's Questionnaire variable. For the high depression subpopulation, there was also no significant diference between the three treatments on any variable.

(c) Doctor's Disposition: The diazepam group was significantly more improved than the placebo group for the following questions: (1) Whether the patient would like to stay on the same medication and (2) what helped most. Diazepam was favored (trend) over buspirone and placebo on the subject's evaluation of improvement. These analyses were for all of the efficacy patients from baseline to endpoint. For the high depression subpopulation, there were no differences for any of the variables among the three treatment groups.

(d) Sleep evaluation:

For all efficacy patients from baseline to endpoint, the diazepam patients were significantly more improved than the buspirone patients for items which ask how long it takes one to fall asleep and how often the subject awakens. Buspirone was favored over placebo on the "type of sleep" or question where less of the shift towards deep sleep is interpreted as improvement, however, this interpretation that less deep sleep represents improvement is not self-evident and its relationship to the diseased state is not clear.

For the high depression subpopulation, the diazepam subjects were significantly more improved on the

"how often awakened" question and diazepam showed a trend over placebo on this question as well. There were no other significant differences for this high depression subpopulation on the sleep variables.

(e) Symptom Checklist: For the overall efficacy analysis from bas line to endpoint, placebo was favored by a trend over diazepam for the Inferiority and Interpersonal Sensitivity Factors. For the high depression subpopulation, buspirone was favored over diazepam for the tension factor and placebo was favored over diazepam for the tension factor.

(f) Profile of Mood States:

There were no significant differences among the three treatment groups from baseline to endpoint for the overall efficacy population. For the high depressed population there was a trend for diazepam over placebo on the Vigor factor.

(g) Raskin-Covi Scale

For the overall efficacy population, there were no significant differences among the three treatments on the Raskin-Depression Scales or the Covi-Anxiety Scale total scores from baseline to endpoint except that diazepam was favored over buspirone on the Covi Item No. 3 (secondary symptoms of depression).

For the high depression subpopulation, the three treatment groups did not differ significantly on the Raskin or Covi total score from baseline to endpoint. There are also no differences among the three treatment groups on any of the six Raskin-Covi items.

(4) Side effects:

(a) General

25 (63%) of the buspirone patients, 30 (75 %) of the diazepam and 14 (35%) of the placebo patients had at least one adverse experience during the study. Fifteen (38 percent) of the buspirone subjects, 18 (45%) of the diazepam subjects and 7 (18%) of the placebo subjects had an adverse experience which led to dosage reduction or discontinuation. It is noted that four of the buspirone patients experienced "excitement."

One buspirone subject (patient 589) was noted as having severe muscle spasms which began apparently before the drug was prescribed. The same patient continued to have mild muscle spasms for 22 days but it also appears that this was not while the patient was on the drug but prior to entry in the study. There was also an adverse experience listed as "muscuskeletal aches/pains" but I cannot find this on the individual patient listing.

(b) Laboratory

It was the sponsor's conclusion that none of the abnormalities which occurred (values outside the normal range) were considered to be clinically significant. Looking over the data, I tend to agree with the sponsor's conclusion.

(c) Physical examination

The only normal to abnormal examination which appears to be of clinical significance is one subject (594) who had a macular rash bilaterally on the forearms at the end of the study.

(d) EKG

Four subjects on buspirone had EKG abnormalities at endpoint. One subject on buspirone had a normal EKG and after one week on drug had diffuse T-wave flattening compatible with hypokalemia or drug effect. The EKG was repeated after the subject was off drug off six weeks and the abnormality was still present. The patiert has hypertension and is on multiple medications. The changes were not considered to be clinically significant. Three other patients on buspirone had abnormalities at baseline which were considered to be unchanged during the study on drug.

(e) Vital signs

One subject had bradycardia of 56 (No. 237). A couple of subjects experienced a mild lowering of blood pressure which was still within the normal range. It is noted that four subjects on buspirone had dizziness, and one had lightheadiness but it is not known whether this was any relation to hypotension. The sponsor's conclusion was that none of the changes in vital signs was clinically significant.

(5) Evaluation and Comments This study generally was non-discriminatory among the three treatment groups for any major efficacy variables. However, there were some analyses that favored diazepam. This study would not support the efficacy of buspirone in the treatment of Generalized Anxiety Disorder.

e. Study No. 1012

(1)

(2) Description of patients:

120 patients were randomized into the study: 117 (40 buspirone, 39 diazepam, and 38 placebo) patients were included in the efficacy analysis. Three buspirone, 4 diazepam and 5 placebo subjects were excluded from the efficacy analysis. The maximum daily dosage for each treatment group expresses an average appears in Appendix I. All subjects met the DSM III criteria for Generalized Anxiety Disorder.

33 (83%) of the buspirone, 31 (79%) of the diazepam and 26 (68 percent) of the placebo efficacy patients were considered to be in the high depression subgroup. 65% of the buspirone group (26 patients), 85 percent of the diazepam group (33 patients) and 66 percent of the placebo group (25 patients) stayed in the study for the four full weeeks.

4 of the buspirone subjects, 8 of the diazepam subjects and 5 of the placebo subjects received concomitant medication. Only one diazepam and one placebo patient received medications that they had not been receiving upon entry into the study. Although some of the medications such as synthyroid would be expected to possibly have an effect on the variables measured in the study, these instances seem randomly distributed among the three treatment groups and probably had no effect on the study outcome.

(3) Outcome

(a) Ham-A and-Ham D: see Appendices II and III for Ham A and Ham D total scores (actual) by week for each of the three treatment groups.

For the overall efficacy population from baseline to endpoint for Ham-A the diazepam group was significantly better than placebo. Diazepam was better than buspirone for the total score

and Somatic factor and showed a trend over buspirone for the Psychic factor. There were no significant differences for buspirone over placebo for either total score or for the Psychic and Somatic factors. For the Ham-A items, diazepam was better than placebo only for item #4, insomnia. Buspirone was not significantly better than placebo for any Ham-A items. Diazepam was better than buspirone for item 3 fears, item 4 insomnia, item 7 somatic/muscular, and #10 respiratory.

For the high depression subpopulation diazepam was better than placebo for the somatic factor with the trend favoring diazepam for the total score. Diazepam was significantly better than buspirone on the somatic factor and total score (trend). Diazepam was better than placebo for item #4 insomnia and diazepam was better than buspirone for item 4 insomnia and item 10 respiratory.

For the Ham-D scores from baseline to endpoint for all efficacy patients, diazepam was significantly better than placebo for total score, Anxiety Somatization Factor, and Sleep Disturbance. Diazepam was significantly better than buspirone for the Sleep Disturbance Factor. There were no significant differences for buspirone over placebo for Ham D total score or any of the factors. For Ham D items from baseline to endpoint, diazepam was significantly better than placebo for items 4, 5, and 6 insomnia early, middle and late, item 18 diurnal variation and item 21 obsessive/compulsive. Diazepam was better than buspirone for items 4 and 6 insomnia early and late, and item no. 18 diurnal variation. Buspirone was not significantly better than placebo for any Ham-D items.

For Ham-D for the high depression subpopulation, diazepam was significantly better than placebo for the Sleep Disturbance Factor. For Ham-D items for the high depression subpopulation, diazepam was significantly better than placebo for items 18 diurnal variation and 21 obsessive/compulsive. Diazepam was better than buspirone for No. 18 diurnal variation. Busperone was not significantly better than placebo for any of the Ham-D items for this high depression subpopulation.

(b) Physician's Questionnaire

The diazepam group showed a trend towards more improvement than the placebo group for Doctor's Opinion of Subject's Change and Subject's Opinion of Subject's Change. The diazepam group was significantly better than the buspirone group for the same two variables. There were no differences among the three treatment groups for the global psychopathology rating on the Physician's Questionnaire. The only significant treatment difference for the high depression subpopulation was a significant difference for diazepam over buspirone on the Doctor's Opinion of Subject's Change.

(c) Doctor's Disposition

Diazepam was significantly better than placebo for the drop-out question and the subject's evaluation of improvement with a trend towards significance for the "stay on same medication" question. Diazepam was better than buspirone for the Subject's Evaluation of improvement, the Physician's Evaluation of improvement, and the "stay on same medication" question.

For the high depression subpopulation, diazepam showed a trend towards being significantly better than placebo for the Subject's Evaluation of improvement. Diazepam was better than buspirone for the Subject's Evaluation of improvement, the Physician's Evaluation of improvement, and the "stay on same medication" question.

(d) Sleep Evaluation

Diazepam was better than placebo and buspirone for the "how long to fall asleep" and "how often awakened" questions. The diazepam group showed more of a shift towards deep sleep than placebo or buspirone. The high depression subpopulation had similar results.

(e) Symptom Checklist

For the overall population the only variable that differed significantly among the treatments from baseline to endpoint was the Somatization Factor: Diazepam was better than placebo. Diazepam was also favored over placebo significantly for three SCL items (#26, difficulty falling asleep, #16, heavy

feeling in arms or legs and #47 feeling weak in parts of your body). Diazepam was significantly better than buspirone for 7 items on the SCL.

For the high depression subpopulation, there were no signficant treatment differences among the buspirone, diazepam or placebo groups for either total score or factor scores. Diazepam was favored over placebo for two items and over buspirone for four items.

(f) Profile of Mood States:

For the overall efficacy analysis from baseline to endpoint, the diazepam was significantly better than placebo and buspirone on the Vigor factor. There were no other significant treatment differences in the total scores or the factors. Diazepam was favored over placebo on items such as active, energetic, alert, full of pep, vigorous, friendly. Diazepam was also favored over buspirone for several items. For the high depression subpopulation, the results were similar, with diazepam favored over placebo and buspirone for the Vigor factor.

(g) Raskin-Covi Scale:

For the overall analysis, there were no significant treatment differences on the Raskin-Depression or Covi-Anxiety Scale total scores. Diazepam was better than placebo on the Raskin item No. 2 secondary symptoms of depression and better than buspirone on the Covi item No. 3 somatic complaints. For the high depression subpopulation, the three treatments did not differ significantly on any of the six Raskin-Covi items or total score.

(4) Side Effects:

(a) General

17 (40%) of the buspirone patients, 24 (56%) of the diazepam patients, and 18 (42%) of the placebo patients experienced at least one adverse event. Seven (16%) of the buspirone patients, 15 (35%) of the diazepam and 14 (33%) of the placebo patients experienced an adverse event requiring dosage adjustment.

There was one instance of severe muscle spasms in the buspirone group. This adverse event began after 19 days on drug.

(b) Laboratory tests:

The sponsor's opinion was that none of the abnormalities outside the normal range was considered to be clinically significant. There were three patients on buspirone with high glucose (approxiamtely 160). After perusing the data, I tend to agree with the sponsor's conclusion.

(c) Physical Examination

Norma to abnormal physical examinations were not considered to be clinically signficant. They included a diophoretic general appearance, increased bowel sounds, trauma (car accident), and tender epigastrium.

(d) EKG

There were three abnormalities on EKG. All of these were also abnormal at baseline.

(e) Vital signs

There were no significant changes in pulse or blood pressure that the sponsor noted. Two patients had a pulse of 50 while on buspirone. There appeared to be some mild blood pressure drops which were still within the normal range but greater than 15 mm of Hg.

(5) Evaluation and Comments

This study was generally negative for supporting the efficacy either buspirone or the comparison drug, diazepam, in the treatment of Generalized Anxiety Disorder. There were some scattered items and other variables which favored diazepam, only some of which appeared to be due to diazepam's sedative properties.

2. Active Drug Control Trials

There were six individual studies in which either clorazepate or diazepam was used as a comparative agent in controlled trials. These studies were conducted according to identical protocols, except for the comparative agent and the dose. Psychometric assessments used in all studies included the Hamilton Anxiety Scale, Hamilton Depression Scale, Physician's Questionnaire, Doctor's Disposition, Lippman-Rickels, Symptom Checklist, Profile of Mood States, Raskin-Covi Scales, and Sleep Evaluation. All subjects were required to have a primary diagnosis of anxiety neurosis as listed in the DSM II classification. Retrospectively, all patients included in the efficacy analyses were rediagnosed according to the Generalized Anxiety Disorder of DSM III. The symptoms required for inclusion were checked off in the case report forms were cross-referenced to DSM III criteria for Generalized Anxiety Disorder. The Raskin Depression Scale total was required to be less than the Covi Anxiety Scale total score. Safety Assessments included vital signs, clinical laboratory, physical examinations, EKGs and recording of adverse reactions. All of the studies were 4 week double-blind, randomized parallel group design. Each of the studies had a double-blind extension period during which patients could either extend on their previous treatment for twenty weeks or switch to the opposite active treatment for twenty four weeks.

For the buspirone vs diazepam studies, both active drugs were administered from daily doses of 10 mg to 50 mg. For the buspirone vs the clorazepate studies, the dose of buspirone was between 10 and 60 mg and the dose of clorazepate was between 15 and 90 mg daily.

Subjects were excluded for missing HAM A for week 1 or week 2, duration of study medication less than 7 days, or use of another investigational drug, antidepressant or neuroleptic during the treatment period.

The analyses reported were based on data which reflects the last available rating for study participants who dropped out. In other words, subjects who dropped out during the study but who were included in the efficacy analysis would have there last rating carried forward for subsequent weeks.

The hypothesis which were to be tested in these studies were the following: buspirone is efficacious in the treatment of anxiety neurosis, anxiety accompanied by depression that is also responsive to buspirone, and buspirone causes significantly less sedation than diazepam.

a. Buspirone vs Clorazepate Studies

Table IV below shows the numbers of patients enrolled in each individual study and the number which was included in the efficacy analysis. These studies were analyzed both individually and as a composite.

TABLE IV

BvC Studies	Enrolled		Included in Efficacy Analysis	
	B	C	B	C
1029	106	33	98	31
1032	50	16	30	16
1041	99	32	90	28
Composite	255	81	218	75

(1) Investigators:

(a)

(b)

(c)

(2) Conduct of Studies

All of the studies were conducted in a similar manner as described above. Study #1029 administered buspirone at a dosage of 10-30 mg/day while the other two studies used buspirone at a dose from 10 to 50 or 60 mg/day. See Appendix I for the mean maximum daily dose of subjects in each study by treatment group. 71 % of the buspirone subjects and 73% of the clorezepate subjects had a final efficacy rating at week 4.

(3) Outcome:

Analyses were performed both for the overall efficacy population and the high depression subpopulation. Diazepam and clorazepate were judged to be equivalent in efficacy on all measures for the overall population and the high depression subpopulation except for the HAM A in the high depression subpopulation and the POMS for the overall efficacy analysis (no overall conclusion was possible due to a significant study by treatment interaction). The sponsor states that the power of the statistical tests was sufficient to detect a difference between treatment groups if one had existed. All treatment groups were judged to be significantly improved from baseline to endpoint.

From the sleep evaluation variables, it was determined that the clorazepate treated patients took less time to fall asleep and awakened less frequently than the buspirone treated patients. The sponsor attributed these differences to the sedative properties of clorazepate. 19 (41%) of buspirone and 34 (45%) of the clorazepate patients were included in the high depression subpopulation.

(4) Side Effects

(a) General

All subjects entered into the study were included in the safety analysis. 28% of the buspirone patients and 37% of the clorazepate patients had at least one adverse experience requiring either dosage reduction or discontinuation. It is noted that in the study #1029 that patient # 22 experienced rigid stiff muscles after one day on drug which was a severe reaction but judged not to be related to the test drug by the investigator. When the composite report of buspirone vs clorazepate is considered, there are significantly more clorazepate subjects than buspirone subjects who experienced drowsiness (21 of 81 clorazepate patients), 26%; 25 of 255 buspirone patients, 10%).

(b) Laboratory

All abnormal values were reviewed by the Medical Monitor, and none were considered clinically significant.

(c) Physical Examinations

Sponsor states that there were no clinically significant abnormalities at endpoint that did not exist at baseline.

(d) EKG

In study # 1029, patient # 29 on buspirone had sinus rhythm, accelerated A-V conduction, and complete left bundle branch block at baseline. After 4 weeks on drug, the subject had atrial fibrillation, nonspecific low voltage, and complete left bundle branch block.

Serial comparison indicated no clinically significant difference between the two tracings as determined by the investigator.

Patient # 82 in study #1029 was admitted to the study with a diagnosis with myocardial insufficiency and a myocardial infarction approximately 3 years prior to participation in the study. At baseline this subject had PVCs and myocardial ischemia. After 4 weeks on the study the patient dropped out, was hospitalized for chest pains and found to have an acute MI. The investigator judged that this adverse event was not related to drug administration. This subject is a 41 year old woman.

(e) Vital Signs

The sponsor states that there were no clinically significant changes in vital signs (pulse or blood pressure).

b. Buspirone vs Diazepam Studies

(1) Investigators

(a)

(b)

(c)

(2) Description of Study

Table V below, taken from the sponsor's submission presents a number of patients randomized into each treatment group and the number included in the efficacy analysis.

TABLE V

BvD Studies	Enrolled		Included in Efficacy Analysis	
	B	D	B	D
1000	105	35	88	33
1048	51	15	43	13
1049	89	29	77	23
Composite	245	79	208	69

Appendix I describes the mean maximum daily dosage of medication for each treatment group in the individual studies which make up this composite. Fifty percent (103) of the buspirone subjects and 58% (40) of the diazepam subjects were included in the high depression subpopulation (HAM D total score of 18 or greater).

Sixty-nine (140) 69% (144) of buspirone subjects and 73% (50) of the diazepam subjects completed the entire 4 weeks of the study.

(3) Outcome:

In both treatment groups, there was significant improvement measured on all variables. Buspirone was comparable to diazepam in this study.

For the Physician's Evaluation Question on the Doctor's Diposition, diazepam treated patients showed significantly more improvement than buspirone treated patients. Buspirone appeared to comparable to diazepam both in overall efficacy and for the subpopulation of high depression subjects for the remainder of the study variables.

(4) Side Effects:

(a) General

Thirty-six % (88) of the buspirone subjects and 51% (40) of the diazepam subjects who were included in the safety analysis (all patients) had at least one adverse experience.

Eighteen % (44) of the buspirone subjects and 28% (22) of the diazepam subjects had at least one adverse experience which required a dose reduction or discontinuation.

Five % (12) of the buspirone subjects and 35% (28) of the diazepam subjects experienced drowsiness which was a statistically significant difference.

Patient # 50 in study 1000 experienced severe rigid/stiff muscles after 9 days on drug (20 mg buspirone). The investigator judged the reaction to be of "unknown" relationship to the test drug. Patient # 125, also in study 1,000 experienced rigid/stiff muscles of mild severity after 1 day on 10 mg of buspirone. The investigator also judged this reaction to be unknown relationship to the test drug. It is noted that one patient on buspirone (096) experienced hypotension and another (014) experienced tachycardia.

(b) Laboratory

None of the abnormalities outside of normal range were considered clinically significant after review by the sponsor's Medical Monitor.

(c) Physical Examination

There were no abnormal physical exam nations at endpoint of subjects who were normal at baseline which were considered to be clinically significant.

(d) EKGs

None of the changes in EKG were considered to clinically significant. This will be further considered in the overall safety review.

(e) Vital Signs

The sponsor's states that no clinically significant changes were detected in pulse or blood pressure although there were numerous changes beyond 15 mm Hg in blood pressure or pulse variations greater than 10 beats per minute.

C. Evaluation and comments:

Active Control Studies:

The composite studies did not include a placebo group for comparison. Because of this, there is no way of knowing whether the active treatment groups, which both were significantly improved from baseline, would have been superior to placebo. Because Generalized Anxiety Disorder is a condition with a variable course and often a high spontaneous remission and/or response to placebo, it is difficult to judge a drug's performance without comparing it to a placebo standard in that study. The active control group cannot be compared accurately to placebo groups in other studies of anxiety, since the placebo response rate is highly variable.

These studies are, however, supportive of the efficacy of buspirone in Generalized Anxiety Disorder. The results of the active control studies do show a general comparability of buspirone to the marketed anxiolytics, clorazepate and diazepam.

There were instances of "rigid/stiff muscles" in the composite studies, but its relationship to parkinsonian side effects possibly caused by buspirone is unknown. The safety data will be discussed further in a overall safety review.

VIII. Overall Evaluation of Efficacy Trials

The two Goldberg studies and the Rickels study constitute the evidence demonstrating efficacy of buspirone in Generalized Anxiety Disorder. The Feighner and Smith studies did not discriminate well between the active drugs (buspirone and diazepam) and placebo. These studies did have some variables in favor of diazepam rather than buspirone, some but not all of these were related to diazepam's sedative properties. The active control studies are supportive of buspirone's efficacy as compared to diazepam and clorazepate, in the treatment of Generalized Anxiety Disorder.

One of the concerns in reviewing the submission was the high depression subpopulation included among the overall study participants who had Generalized Anxiety Disorder. There was a substantial number of subjects with HAM-D's greater than 18 in all treatment groups in all of the studies. This brings up the question as to the appropriate primary diagnosis. There was considerable overlap in the symptoms of depression and anxiety, and this is reflected in the rating scales used, the HAM-A and the HAM-D. I asked the sponsor to compare an analysis which would consist of the frequency distribution by treatment group of patient baseline scores for HAM A item # 6 (Depressed Mood) for the high depression subpopulation. (see Appendix IV)

In other words, it is possible for a subject to be anxious and score high enough on the HAM-D to obtain a rating of 18 without being clinically depressed. Such a frequency distribution should allow me to check whether the subjects included in such a high depression subpopulation, defined by HAM-D greater than 18, are actually depressed by some measure. Item 6 on the HAM-A is rated on a 5 point scale from 0, not present to 4, which is very severe. For study # 764, all subjects who were included in the high depression subpopulation had HAM-A item 6 scores of at least 2 (moderate). In study # 994, there were 24 subjects in all treatment groups in the high depression subpopulation who did not have a score of at least 2 but had either zeros or ones (mild). For study # 995 there were 13 subjects in all treatment groups who were included in the high depression subpopulation who did not have at least a 2 on the HAM D item 6. Even though the frequency distribution demonstrates that it is possible to have a HAM-D score of 18 or greater without being more mildly depressed, the majority of the subjects in the high depression subgroup did have baseline HAM-A item 6 scores of 2 or greater. Most were in the moderate to severe range. Only one was in the "very severe" range.

There was a requirement that subjects have a primary diagnosis of anxiety neurosis even though depression was allowed to be present. There was also a requirement for studies 994 and 995 that the Raskin total score be less than the Covi total score. However, these scales are so subjective that such a procedure does not guarantee the subjects are not primarily depressed rather that primarily anxious.

In reviewing this data, it is my impression that the majority of study subjects did have a primary diagnosis of anxiety and that a considerable number of participants, sometimes the majority of participants had Mixed Anxiety/Depression syndromes. Also, the fact that the study population responded to diazepam as well as buspirone indicates to me that the participants were probably primarily anxious rather than depressed.

A question is raised as to whether subjects without depression also respond to buspirone. A brief analysis done by the sponsor on major outcome variables confirms that subjects who had HAM D totals of less than 18 also responded to the study drug in the three pivotal studies.

The sponsor has also claimed that buspirone is effective in the presence of depression. There is a question as to whether buspirone is different from known antianxiety agents in having increased efficacy for Mixed Anxiety/Depression Syndromes. Appendix V shows results from the placebo controlled trials which demonstrated the efficacy of buspirone according to whether buspirone and/or diazepam was effective for various measures for both anxiety and depression. In general, diazepam was comparable to buspirone in its positive effects in the "high depression" population, even though there are a few instances when buspirone seemed efficacious but diazepam did not. More studies would be necessary to confirm the hypothesis that buspirone has an improved efficacy for subjects with Mixed Anxiety/Depression syndromes compared to marketed antianxiety agents. Data presented in this NDA application did not clearly support this contention.

The safety data here indicates that buspirone may be less sedative than comparative agents, diazepam and clorazepate. This will be addressed further in the safety section.

IX. Special Studies

A. Neuroendocrine Studies:

1. Study #1324:

a.

b. Study Design/Rationale:

This study was designed to examine the effects of buspirone on human growth hormone and prolactin when administered in single oral doses to normal volunteer adult male subjects. There were two parts to the study. In the first part, each of 8 subjects received the followng single doses of drug at weekly intervals: 30 mg, 60 mg, and 90 mg buspirone, and placebo. In the second part, 6 subjects (5 of the above subjects participated in the first part and one new subject) each received 5, 10, and 15 mg of buspirone at separate treatment sessions. For both parts of the study, blood samples were drawn for assays of prolactin, growth, normone, cortisol and buspirone. Blood specimens from the first part were also assayed for aldosterone. These hormones were determined at the following time points relative to dosing: - 0.5 hours, - 0.25 hours, 0 time, 0.25 hours, 0.5 hours, 1 hour, 1.5 hours, 2 hours, and 3 hours.

c. Outcome:

The sponsor calculated the mean adjusted area under the plasma concentration vs time curve (R AUC) for prolactin for each dosage level as shown in Table V below. Six to eight subjects were used for each determination. The data contained in Table V is derived from a total of 9 subjects.

Table V

Prolactin (ng/ml)

Buspirone Dose (mg)	0	5	10	15	30	60	90
Mean R AUC	1.02	1.09	1.28	1.40	3.10	5.52	6.31

The sponsor's results states that 5, 10, 15, and 30 mg of Buspirone does not differ significantly from placebo in its effects on prolactin secretion. The 60 mg and 90 mg dosage levels, however, were not different from each other but did induce significantly higher prolactin levels than placebo.

Appendix VI shows the individual prolactin levels after increasing single acute doses of Buspirone. Normal prolactin levels are approximately 1 to 20 ng per ml. According to this table, the level of prolactin appears to be increasing for some study subjects at the 30 mg level and above. One study subject of the six tested at the 15 mg level had an increase of prolactin. This subject also had a mild increase after the 10 mg dose (subject #24, who was also subject #9 in the part of the study done at the higher dosage range).

The sponsor states that the results of analyses of variance of the R AUCs for human growth hormone at the different dosage levels showed no significant differences among any of the Buspirone dosage groups.

The sponsor states that there was no apparent effect on plasma, cortisol or aldosterone levels for any of the single oral doses of Buspirone.

2. Study 529:

b. Rationale/Design:

This was a double-blind, randomized cross-over study of 10 healthy male subjects from 21 to 23 years which determined each subjects prolactin response after a single dose of the following five treatments: Buspirone 25 mg, Buspirone 50 mg, Buspirone 100 mg, Sulpiride 200 mg, and placebo. There was a drug free interval of at least 5 days between each treatment period. Normal values for serum prolactin in this investigators laboratory are 30 ng per ml or less. Prolactin levels were measured at time 0, 1 hour, 3 hours, and 5 hours after drug administration.

c. Outcome:

The sponsor states that pair wise comparisons of mean prolactin levels indicate that there were no significant differences between placebo, 25 or 50 mg of buspirone at 1 or 3 hours. Buspirone 100 mg was significantly different from placebo and the two lower doses of buspirone. 200 mg of Sulpiride produced the highest increases and was significantly different from all other treatments.

The area under the curve for prolactin levels was calculated by the sponsor for each study subject from 0 to 5 hours as shown in Table VI below.

Table VI

Prolactin (ng/ml)

Treatment	Placebo	25 mg Buspirone	50 mg Buspirone	100 mg Buspirone	200 mg Sulpiride
AUC (mean)	104.80	117.70	158.90	289.80	647.15

Prolactin levels following sulpiride were significantly higher than for all the other treatments. Prolactin levels following 100 mg of Buspirone were significantly higher than the lower dosages and placebo. Prolactin levels after 25 and 50 mg of Buspirone were not signficantly different from placebo.

Appendix VII (taken from the sponsor's submission) shows the individual patient data. As can be seen, there is considerable individual variation in the response to both different levels of Buspirone and to the 200 mg dose of sulpiride.

3. Evaluation and Comments Concerning Neuroendocrine Studies:

The sponsor's conclusion from these studies is that buspirone should not affect plasma prolactin levels when used at the recommended dosage levels for anxiety disorders. The proposed dosage is from 15 to 60 mg daily with a usual daily dose from 20 to 30 mg per day in divided doses. The sponsor further states that no cases of gynecomastia or galactorrhea occurred in any of the clinical studies.

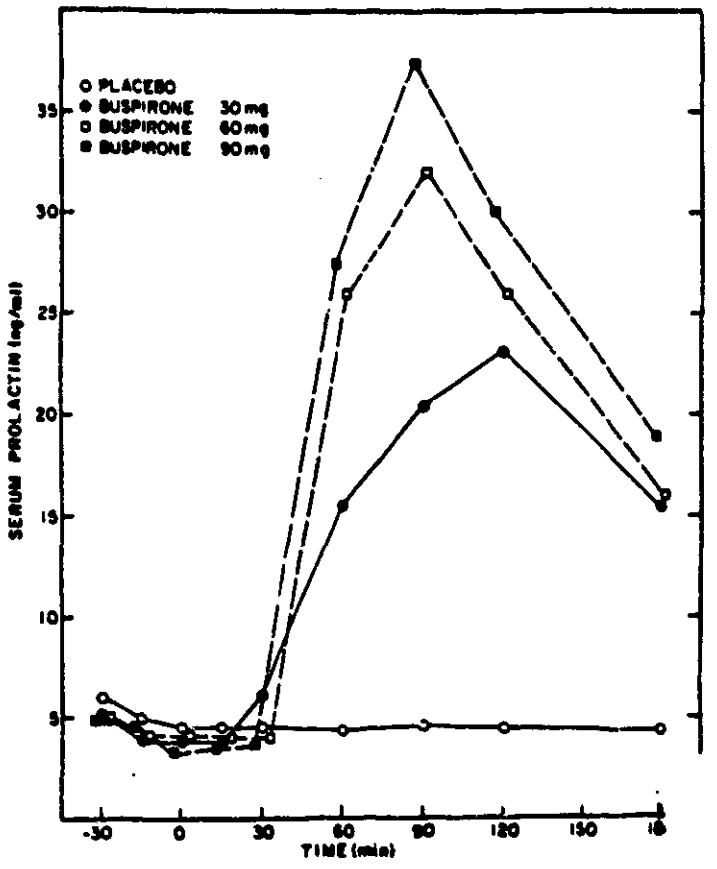
There have been a small number of subjects studied as to their plasma prolactin response to buspirone and these investigations have only been for single acute dosages. There is no information concerning plasma prolactin levels during chronic use of buspirone within the therapeutic dosage range.

In study, the prolactin level did not increase until after acute buspirone dosages of 100 mg. Comparing the prolactin levels after 100 mg of buspirone and 200 mg of sulpiride, we can see that the increased prolactin levels after 100 mg of buspirone certainly are not maximal. In study 10 subjects were included. For study, a total of 9 subjects were participants, with 6 to 9 subjects at each dosage level tested.

In study, one subject (#24) of 6 at the 15 mg dosage level did experience an increase in prolactin. There seems to be considerable individual variation, and we do not know what the results would have been if there had been a larger sample.

In published study (Journal of Clinical Psychiatry 43:12 (Sec. II) - December, 1982), reported on the part of the study that included Buspirone levels of 30, 60, and 90 mg. Dr. Meltzer concluded that each level increased plasma prolactin, and that there was a dose related increase in prolactin for 1 to 3 hours. See the graph below which is taken from that paper.

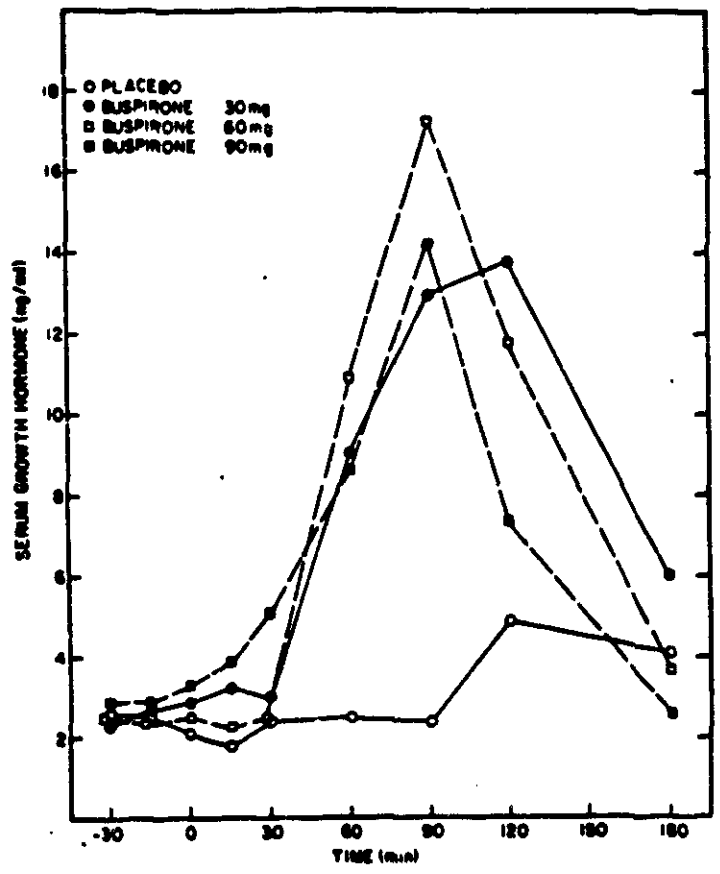
Figure 1. Effect of placebo and buspirone (30, 60, and 90 mg) on plasma PRL levels in 8 normal volunteers.



likened the increases seen after these dosages to that after 25 or 50 mg of i.m. chlorpromazine in normal volunteers. He further cited preclinical evidence which is consistent with its action as a dopamine receptor antagonist. There are different mechanisms by which prolactin can be increased, but the evidence is here that prolactin is increased by a dopaminergic blockade at the pituitary level.

, results were different from that of the sponsor since he reported a dose-related increase in growth hormone among his study population (except for two subjects who had no increase in plasma growth hormone following buspirone administration at any of the doses). See the figure below which was taken from this article.

Figure 2. Effect of placebo and buspirone (30, 60, and 90 mg) on plasma GH levels in 8 normal volunteers.



It is difficult to make a conclusion upon the limit data provided. However, from 's study it appears that some subjects can have an increase in prolactin within the therapeutic dosage range, even though this increase does not appear to be maximal. Only longer term studies in larger numbers of subjects will provide more of an answer to the question of whether buspirone is a significant dopamine receptor blocker when used in therapeutic dosages.

B. Functional Impairment and Abuse Potential Studies:

These studies will be reviewed by Dr. Frank Vocci of the Drug Abuse Staff and thus will not be detailed here. There were six functional impairment studies by four separate

investigators. Functional impairment both with and without alcohol was measured by various performance tasks. The sponsor concluded that buspirone does not cause functional impairment. It causes significantly less impairment than diazepam or lorazepam when administered either alone or in combination with alcohol.

There were two human abuse potential studies conducted by . Subjects were not able to distinguish between buspirone and placebo. A significant preference for the positive control, methaqualone and diazepam over placebo was statistically significant.

X. Overall Safety Review:

A. Treatment Emergent Side Effects for the Eleven Controlled Efficacy and Safety Trials:

The following is a report of the adverse events during the five buspirone vs diazepam vs placebo trials, the three Buspirone vs diazepam trials and the three Buspirone vs. clorazepate trials.

1. Those discontinuing due to adverse effects: Table VII below shows the number of subjects in each treatment group who discontinued due to adverse events and also those who had side effects which significantly interferred with functioning or outweighed therapeutic effects. This table is taken from the sponsor's submission.

Table VII

	Buspirone N = 748	Diazepam (N = 325	Clorazepate (N = 61)
# Discontinuing due to adverse effects	57 (8%)	22 (7%)	9 (11%)
# Not discontinuing but having adverse effects which significantly interfered with functioning or outweighed therapeutic effect	30 (4%)	27 (9%)	8 (11%)

Appendix VIII taken from the sponsor's submission, shows the types of adverse reactions in those patients discontinuing due to side effects during the Part I (4 week studies). This table does not always correspond to other such data listings in this submission. As Appendix VIII notes, when subjects had multiple side effects, the one that the investigator considered to be drug related or most severe was used to prepare this incidence table.

DL-1.1 and 1.2 of the sponsor's submission in Vol. 1.67, contain individual patient descriptions of subjects who discontinued due to adverse events. Selected subjects are described below.

Subject 436 in Study #996, a 39 year old female experienced a severe "buzz or high" on buspirone. Upon discontinuation of the medication, the symptoms subsided. It is noted that patient 50 in Study #1000, a 35 year old male, had rigidity of his jaws among his side effects. His total daily dose of buspirone was 5 mg q.i.d. The rigidity and the other symptoms subsided upon drug discontinuation. There are approximately eight patients on buspirone who discontinued who reported a syndrome of severe excitement, insomnia and restlessness which was sometimes associated with vivid dreams.

Subject 34 in Study #1041, a 34 year old female, experienced a CVA during Part II of the study. She was S/P polio and asthma and on multiple medications. Subject 82 in Study #1029 was a 41 year old female experienced an MI during Part I on buspirone. She had a history of hypertension and angina over the previous year. She also had a previous myocardial infarction. One subject in study Part I discontinued due to euphoria. There are five cases of subjects discontinuing due to restlessness during Part I on Buspirone.

2. <u>Overall Instances of Adverse Reactions in the Eleven Study Composite (Treatment Emergent Events</u>

Appendix IV, taken from the sponsor's submiss on, shows the buspirone adverse reactions incidences as compared to placebo. Appendix V taken from the sponsor's submission, also shows the adverse events but here they are divided into mild, moderate and severe. It is noted here that motor restlessness is subsumed under the synonym "nervousness".

The sponsor states that dizziness, headache, diarrhea and nervousness were the side effects which had a significantly greater incidence for buspirone than placebo. When sedation is defined according to primary terms of "drowsiness" and/or "fatigue" the sponsor states that there was no significant difference between sedation produced by buspirone (11%) and placebo (13%). In contrast, diazepam produced a 40% incidence of drowsiness and/or fatigue while clorazepate produced a 33% incidence of these effects.

3. Adverse Reactions Occurring in Domestic Studies Contained in Other Sections of the NDA:

Many of these studies were done at much higher dosages than in the controlled clinical studies designed for demonstration of efficacy. The side effects seen at higher dosages include euphoria, a "rush" of tingling sensation, akathisia, muscle rigidity, excitement and insomnia, restless, palpitations, vomiting, facal flushing, muscle spasm, bradycardia, sedation, heavy perspiration.

4. Adverse Reactions Occurring in Patients Enrolled in Controlled Clinical Studies Conducted Outside the United States:

Appendix XI, taking from the sponsor's submission, shows the incidence of adverse reactions in these nine foreign, controlled clinical studies.

B. Laboratory Examinations:

The sponsor has compiled tables of normal to abnormal changes in laboratory tests for each treatment period. No clinically significant changes outside of the normal range were found upon the sponsor's review. See Appendix XII, taken from the sponsor's submission, for comparative incidences outside of the normal.

In the 11 study composite, buspirone, diazepam, and clorazepate all had higher incidences of increased basophil count on the CBC differential. This was not considered clinically significant. For the five study B vs D vs P protocol, the serum glucose results had higher incidence of abnormalities for buspirone, but upon review by the sponsor, these glucose results were not deemed to be clinically significant. One normal male volunteer in study #163 one of the early studies, had an increased SGOT but was considered to have intercurrent illness. The sponsor concludes that there was no significantly important buspirone related changes in any of the studies reported in the NDA.

C. Vital Signs:

The sponsor calculated frequencies for normal to abnormal measurements for pulse and blood pressure and also significant changes from baseline from pulse and blood pressure. The sponsor concluded that there were no significant diffrences from placebo for any of these measures.

In biopharmaceutic study #599, two subjects, each of whom received a single dose of 100 mg of Buspirone, experienced a blood pressure decrease and bradycardia. There were no other clinically significant events reported for any of the studies reported in this NDA.

D. Physical Examinations:

The sponsor presented summary tables of normal and abnormal physical examinations by treatment for both Part I and Part II of the studies. Sponsor concluded that there was no clinically significant normal to abnormal physical examination reports in any of the studies in this NDA.

E. EKGs

Appendix XIII taken from the sponsor's submission, shows the incidence of the EKG abnormalies by treatment for the II study composite. When the normal to abnormal EKGs of subject who were on Buspirone were examined, there were several incidences of minor changes such as ST and T-wave changes or bradycardia, none of which were considered clinically significant.

F. Number of Patients on Long-Term Treatment:

As of December 15, 1982 cutoff for this NDA submission, only 68 subjects had received Buspirone for six months or longer. An update is due from the sponsor which may give more information on long-term treatment.

G. Overall Evaluation of Side Effects:

It was difficult to determine from this set of data whether or not any extrapyramidal effects occurred in the lower dosages. There were some cases of muscle rigidity or muscle spasm and one subject who had rigidity of his jaw. For several patients, there seem to be a syndrome of excitement and restlessness sometimes associated with insomnia, and one wonders whether this might be akathisia. There were no prominent changes in laboratory, EKG, or vital signs. The were some incidences of bradycardia and one wonders whether the dizziness that was reported is related to orthostatic hypertension.

The most important safety issue appears to be the ability of Buspirone to produce dopamine receptor blockade in therapeutic dosages as a measure of its potential for producing tardive dyskinesia.

XI. Overall Evaluation and Recommendations:

1. There are three well-controlled trials (the two studies and the study) which demonstrate buspirone's effectiveness in the treatment of Generalized Anxiety Disorder.

2. Buspirone appears to be generally safe except for the possibility that it may produce tardive dyskinesia when used at high doses long-term. There no known way for evaluating this potential other than by long-term experience in large numbers of subjects. However, it is known that buspirone increases prolactin within the therapeutic dose range in some normal individuals, although not maximally. Buspirone has a prelinical profile as a dopamine agonist/antagonist, and several preclinical tests demonstrate its effectiveness as a dopamine receptor blocker.

   There is a possiblity that larger studies of the acute and chronic effects of buspirone on human serum prolactin levels would shed light on this issue. Thus far, only 19 subjects in toto have been studied as to the effect of acute dosages only of buspirone on serum prolactin.

3. There is a possibility that buspirone may offer some advantages over previously marketed anxiolytics. This will be discussed further in the Drug Abuse Review by Dr. Frank Vocci. However, it appears that buspirone has an incidence of sedation which is comparable to placebo, causes minimal functional impairment either alone of in combination with alcohol, and may have less abuse potential than currently marketed anxiolytics.

4. The evidence submitted does not support any unique effects of buspirone (beyond that of the currently marketed anxiolytics) in the treatment of mixed-anxiety depression.

5. The current draft of this review will be presented to the advisory committee for its discussion on buspirone on September 22, 1983.

Linda R. Kessler, M.D.
Group Leader, Psychopharmacology II

cc:
NDA Orig.
HFN-120
HFN-120/LKessler/
R/D/Ica/9/7/83
Doc. #5909B

APPENDIX I

Mean Maximum Daily Dosage
Caps/day*

Study #	Investigator	B	D	C	P
** 764		5.3	5.0	--	6.1
** 994		4.7	4.4	--	5.6
** 995		4.7	4.3	--	4.8
** 996		4.4	4.5	--	5.0
1012		5.4	4.4	--	5.2
1029		4.0	--	3.6	--
1032		5.1	--	5.1	--
1041		5.3	--	3.8	--
1000		4.1	4.2	--	--
1048		4.5	3.3	--	--
1046		4.5	4.0	--	--

* buspirone, 5mg caps; diazepam, 5 mg caps; clorazepate, 7.5 mg caps

**Placebo controlled studies which demonstrated the efficacy of buspirone

Appendix II
Ham-A Total Scores (Actual)
B. v. D. v. P.

1. All patients

Study#	Treatment	n	Baseline mean	Endpoint means (by wk) 1	2	3	4	Differences from Baseline 1	2	3	4
764											
	Buspirone	18	30.3	22.3	13.8	9.2	6.8	-7.9	-16.4	-21.1	-23.5
	Diazepam	18	25.2	16.9	13.1	9.7	9.2	-8.3	-12.1	-15.5	-16.0
	Placebo	18	28.4	22.7	20.7	21.4	21.6	-5.8	- 7.8	- 7.00	- 6.7
994	Buspirone	66	24.4	19.5	16.6	15.2	14.8	-4.9	- 7.8	- 9.2	- 9.6
	Diazepam	17	26.0	19.0	15.8	15.2	14.4	-7.0	-10.8	-10.8	-11.6
	Placebo	51	24.1	21.8	20.8	21.1	20.3	-2.3	- 3.4	- 3.1	- 3.8
995	Buspirone	57	24.5	20.5	17.0	14.2	13.0	-4.0	- 7.5	-10.3	-11.6
	Diazepam	50	23.6	18.3	16.1	14.0	12.4	-5.3	- 7.4	- 9.6	-11.1
	Placebo	56	24.1	19.5	17.3	17.3	16.2	-4.6	- 6.8	- 6.8	- 7.9
996	Buspirone	29	26.5	22.6	20.1	20.0	19.4	-3.9	- 6.4	- 6.4	- 7.1
	Diazepam	32	25.6	20.4	17.1	16.0	15.7	-5.1	- 8.4	- 9.6	- 9.9
	Placebo	29	24.8	20.2	18.1	18.7	18.8	-4.6	- 6.7	- 6.1	- 6.0
1012	Buspirone	40	26.8	23.0	20.5	19.3	17.5	-3.7	- 6.3	- 7.4	- 9.2
	Diazepam	39	29.2	19.6	16.1	15.4	14.5	-9.6	-13.1	-13.8	-14.7
	Placebo	38	27.6	23.2	20.6	18.4	18.2	-4.3	- 7.0	- 9.2	- 9.4

2. Patients with Ham-D>18

Study#	Treatment	n	Baseline mean	Endpoint means (by wk) 1	2	3	4	Differences from Baseline 1	2	3	4
764	Buspirone	9	35.4	29.2	13.6	9.2	6.3	- 6.2	-21.9	-26.2	-29.1
	Diazepam	8	29.2	20.9	15.5	12.1	10.6	- 8.4	-13.8	-17.2	-18.6
	Placebo	9	32.8	30.7	26.7	26.9	26.6	- 2.1	- 6.1	- 6.0	- 6.2
994	Buspirone	32	27.0	21.9	18.7	17.7	17.3	- 5.1	- 8.3	- 9.2	- 9.7
	Diazepam	34	28.4	22.4	18.6	18.6	18.1	- 6.0	- 9.6	- 9.7	-10.3
	Placebo	43	25.7	23.5	22.5	22.5	21.7	- 2.2	- 3.2	- 3.2	- 4.0
995	Buspirone	39	25.9	21.9	18.4	15.2	14.2	- 4.1	- 7.5	-10.7	-11.7
	Diazepam	35	24.7	20.0	17.7	15.2	13.9	- 4.7	- 6.9	-10.8	-10.8
	Placebo	33	24.7	21.9	20.0	19.6	18.8	- 2.8	- 4.7	- 5.1	- 5.9
996	Buspirone	16	28.6	23.2	21.1	21.1	21.3	- 5.4	- 7.5	- 7.4	- 7.2
	Diazepam	15	26.7	22.6	20.7	18.9	18.6	- 4.0	- 6.0	- 7.7	- 8.1
	Placebo	13	28.5	23.8	21.8	22.8	22.5	- 4.7	- 6.7	- 5.7	- 6.1
1012	Buspirone	33	27.7	24.1	21.3	20.0	17.4	- 3.6	- 6.3	- 7.7	-10.2
	Diazepam	31	30.4	20.2	16.0	15.8	15.0	-10.3	-14.5	-14.7	-15.4
	Placebo	26	28.7	24.0	20.4	16.8	18.5	- 4.6	- 8.4	- 9.8	-10.2

Appendix III Ham-D Total Scores (Actual)

B. v. D. v. P.

1.* All patients

Study#	Treatment	n	Baseline mean	Endpoint means (by wk) 1	2	3	4	Differences from Baseline 1	2	3	4
764											
	Buspirone	18	21.0	16.2	9.3	6.7	5.4	-4.8	-11.7	-14.3	-15.6
	Diazepam	18	19.3	12.1	9.2	7.2	7.4	-7.2	-10.1	-12.2	-11.9
	Placebo	18	28.4	19.3	16.7	16.1	15.7	-2.7	- 4.2	- 3.2	- 3.7
994	Buspirone	66	16.8	14.4	12.6	11.5	11.2	-2.5	- 4.2	- 5.4	- 5.6
	Diazepam	71	18.7	14.2	11.9	12.0	11.8	-4.5	- 6.6	- 6.7	- 6.9
	Placebo	73	18.0	17.0	16.4	16.7	16.1	-1.0	- 1.6	- 1.3	- 1.9
995	Buspirone	57	19.9	16.3	14.4	12.6	12.1	-3.6	- 5.5	- 7.3	- 7.8
	Diazepam	50	19.1	15.5	14.2	12.8	12.1	-3.6	- 4.9	- 6.4	- 7.0
	Placebo	56	19.0	15.8	14.2	14.7	13.7	-3.3	- 4.8	- 4.4	- 5.3
996	Buspirone	29	17.5	15.4	14.8	15.5	15.2	-2.1	- 2.8	- 2.0	- 2.4
	Diazepam	32	18.0	14.8	12.5	13.0	13.2	-3.2	- 5.4	- 5.0	- 4.7
	Placebo	29	18.0	16.0	14.8	14.8	14.5	-2.0	- 3.2	- 3.2	- 3.4
1012	Buspirone	40	22.5	19.5	17.3	16.0	15.3	-3.0	- 5.2	- 6.6	- 7.2
	Diazepam	39	23.2	16.1	14.4	13.9	13.4	-7.0	- 8.7	- 9.2	- 9.7
	Placebo	38	22.1	19.2	17.0	16.7	16.5	-2.9	- 5.1	- 5.4	- 5.6

2. Patients with Ham-D >18

Study#	Treatment	n	Baseline mea	Endpoint means (by wk) 1	2	3	4	Differences from Baseline 1	2	3	4
764	Buspirone	9	29.2	23.8	12.2	8.8	6.6	- 5.4	-17.0	-20.4	-22.7
	Diazepam	8	29.2	18.1	13.4	9.8	8.5	- 8.2	-13.0	-16.6	-17.9
	Placebo	9	32.8	24.3	20.9	20.7	20.8	- 1.3	- 4.8	- 5.0	- 4.9
994	Buspirone	32	22.4	18.7	16.4	15.6	15.3	- 3.8	- 6.0	- 6.8	- 7.1
	Diazepam	34	24.1	18.8	16.2	16.7	16.6	- 5.3	- 7.9	- 7.4	- 7.5
	Placebo	43	21.4	20.6	19.7	19.9	18.9	- 0.8	- 1.7	-11.5	- 5.0
995	Buspirone	39	23.3	19.4	16.7	14.8	13.7	- 4.0	- 6.7	- 8.6	- 9.6
	Diazepam	35	22.2	18.3	16.6	14.6	13.9	- 3.9	- 5.5	- 7.6	- 8.3
	Placebo	33	23.2	19.9	17.9	18.2	17.2	- 3.3	- 5.3	- 5.0	- 6.0
996	Buspirone	16	20.7	17.8	16.9	17.0	17.3	- 2.9	- 3.8	- 3.7	- 3.9
	Diazepam	15	22.3	18.2	16.1	16.5	16.4	- 4.2	- 6.2	- 5.8	- 5.9
	Placebo	13	21.6	19.0	17.8	18.2	17.5	- 2.6	- 3.8	- 3.4	- 4.1
1012	Buspirone	33	24.2	20.3	18.4	17.0	15.6	- 3.8	- 5.7	- 7.2	- 8.6
	Diazepam	31	25.2	17.1	15.1	14.6	14.0	- 8.1	-10.2	-10.6	-11.2
	Placebo	26	25.5	21.4	17.8	17.8	17.7	- 4.1	- 7.7	- 7.7	- 7.8

Frequency Distribution by Treatment Group of Patient Baseline Scores for HAM-A Item 6 (Depressed Mood) High-Depression Subpopulation

Study #764

	Baseline Score 0	1	2	3	4	Total
Buspirone	0	0	1	8	0	9
Diazepam	0	0	3	5	0	8
Placebo	0	0	4	5	0	9

Study #994

	Baseline Score 0	1	2	3	4	Total
Buspirone	2	4	20	6	0	32
Diazepam	1	3	25	5	0	34
Placebo	3	11	21	8	0	43

Study #995

	Baseline Score 0	1	2	3	4	Total
Buspirone	1	5	21	12	0	39
Diazepam	2	3	21	9	0	35
Placebo	1	1	18	12	1	33

Study #996

	Baseline Score 0	1	2	3	4	Total
Buspirone	3	4	9	0	0	16
Diazepam	0	9	6	0	0	15
Placebo	0	4	9	0	0	13

Study #1012

	Baseline Score 0	1	2	3	4	Total
Buspirone	0	5	28	0	0	33
Diazepam	0	5	21	5	0	31
Placebo	0	4	19	3	0	26

Appendix V
Comparison of Buspirone and Diazepam on Anxiety And Depression-Related Scores*

Measure	#764	#994	#995
Ham-A Total	B, D	B, D	B, D (trend)
Ham-D Total	B, D	B, D	
Ham-A anxious mood #1	B, D	B, D	D
Ham-A tension #2	B, D	B, D	
Ham-D anxiety, psychic #10	B	B, D	
Ham-D anxiety, somatic #11	B	B, D	
SCL anxiety factor	B, D	B, D	B
POMS tension/ anxiety factor	B, D	B, D	B, D (trend)
Covi total		B, D	B, D
Ham-A, depressed mood #6	B		
Ham-D, depressed mood #1	B	B	

#listing of B or D implies statistical significance over placebo for that treatment group

Appendix VI
Prolactin Levels (ng/ml)
Before and After Single Acute Doses of Buspirone
Study #1324,

Time (hours)

Subject	Buspirone Dose	-.5	-.25	0	.25	.5	1	1.5	2	3
1	0	4.0	4.0	4.0	5.0	4.0	5.0	5.0	6.0	3.0
2	0	6.0	7.0	5.0	4.0	4.0	4.0	3.0	5.0	3.0
3	0	3.0	2.0	2.0	2.0	3.0	3.0	4.0	8.0	3.0
4	0	6.0	4.0	6.0	7.0	8.0	8.0	8.0	8.0	8.0
5	0	2.0	0	0	2.0	1.0	2.0	2.0	2.0	5.0
6	0	10.0	8.0	7.0	4.0	3.0	3.0	4.0	0	3.0
8	0	7.0	6.0	5.0	4.0	5.0	3.0	6.0	6.0	4.0
9	0	8.0	6.0	5.0	5.0	5.0	5.0	3.0	3.0	2.0
20	5	11.1	11.1	11.1	9.7	8.3	8.3	11.1	12.5	13.9
21	5	13.9	12.5	13.9	13.9	22.6	20.4	12.5	8.3	4.2
22	5	5.6	5.9	5.6	8.3	8.3	8.3	9.7	11.1	11.1
23	5	13.9	11.1	11.1	--	9.7	8.3	6.9	8.3	5.6
24	5	11.1	8.3	8.3	9.7	8.3	13.9	16.0	11.1	9.7
25	5	9.5	11.1	8.3	13.9	13.9	16.0	12.5	6.9	8.3
20	10	11.1	13.9	11.1	9.7	11.1	13.9	16.0	18.2	18.2
21	10	11.1	11.1	11.1	9.7	8.3	11.1	9.7	8.3	5.6
22	10	6.9	8.3	8.3	9.7	8.3	11.1	13.9	12.5	12.5
23	10	8.3	6.9	5.6	6.9	6.9	6.9	4.2	11.1	9.7
24	10	9.7	6.9	11.1	11.1	13.9	24.7	26.9	22.6	16.0
25	10	12.5	11.1	11.1	8.3	6.9	11.1	6.9	9.7	11.1
20	15	11.1	11.1	9.7	11.1	11.1	11.1	20.4	16.0	12.5
21	15	8.3	5.6	6.9	9.7	11.1	11.1	11.1	11.1	8.3
22	15	8.3	8.3	5.6	8.3	8.3	11.1	9.7	13.9	13.9
23	15	8.3	5.6	9.7	6.9	8.3	6.9	9.7	8.3	6.9
24	15	12.5	12.5	12.5	11.1	8.3	57.5	35.7	22.6	11.1
25	15	24.7	16.0	13.9	13.9	18.2	16.0	24.7	22.6	11.1

APPENDIX VI (cont.)

1	30	3.0	3.0	2.0	3.0	5.0	29.0	26.0	20.0	8.0
2	30	6.0	5.0	8.0	5.0	4.0	4.0	34.0	45.0	20.0
3	30	4.0	4.0	5.0	4.0	4.0	7.0	12.0	11.0	8.0
4	30	6.0	6.0	6.0	6.0	6.0	7.0	10.0	39.0	41.0
5	30	3.0	2.0	2.0	1.0	2.0	2.0	4.0	10.0	5.0
6	30	8.0	6.0	6.0	6.0	5.0	20.0	15.0	10.0	6.0
8	30	5.0	6.0	4.0	4.0	4.0	14.0	26.0	21.0	13.0
9	30	0.0	8.0	7.0	6.0	6.0	36.0	38.0	29.0	13.0
1	60	4.0	3.0	3.0	2.0	3.0	33.0	32.0	26.0	14.0
2	60	8.0	6.0	7.0	7.0	7.0	34.0	37.0	23.0	14.0
3	60	5.0	5.0	5.0	4.0	4.0	5.0	17.0	6.0	20.0
4	60	4.0	4.0	4.0	5.0	5.0	39.0	46.0	39.0	23.0
5	60	0.0	0.0	1.0	0.0	0.0	19.0	20.0	15.0	6.0
6	60	8.0	6.0	6.0	4.0	4.0	13.0	20.0	17.0	8.0
[illegible]	60	5.0	3.0	3.0	5.0	4.0	24.0	41.0	38.0	21.0
9	60	7.0	7.0	6.0	10.0	19.0	41.0	37.0	30.0	23.0
1	90	5.0	5.0	4.0	6.0	7.0	11.0	34.0	28.0	14.0
2	90	4.0	3.0	5.0	4.0	3.0	31.0	31.0	25.0	16.0
3	90	5.0	5.0	3.0	3.0	3.0	12.0	29.0	30.0	22.0
4	90	7.0	5.0	4.0	5.0	4.0	48.0	47.0	35.0	31.0
5	90	0.0	2.0	0.0	0.0	0.0	31.0	40.0	26.0	17.0
6	90	4.0	3.0	1.0	3.0	4.0	39.0	49.0	38.0	24.0
8	90	7.0	6.0	5.0	6.0	5.0	12.0	32.0	29.0	16.0
9	90	6.0	5.0	5.0	5.0	7.0	43.0	43.0	34.0	24.0

BUSPIRONE - PROTOCOL NO.: 5298US

PROLACTIN LEVEL - DATA LISTING

SUBJECT	PERIOD	DRUG	HOUR0	HOUR1	HOUR3	HOUR5
1	1	100 MG BUSPIRONE	12	26	89	73
1	2	50 MG BUSPIRONE	14	17	21	15
1	3	PLACEBO	16	12	18	12
1	4	200 MG SULPIRIDE	44	255	230	125
1	5	25 MG BUSPIRONE	22	15	15	13
2	1	200 MG SULPIRIDE	15	120	63	44
2	2	25 MG BUSPIRONE	14	18	13	10
2	3	50 MG BUSPIRONE	33	30	49	38
2	4	PLACEBO	17	11	14	13
2	5	100 MG BUSPIRONE	10	87	22	14
3	1	25 MG BUSPIRONE	42	40	32	20
3	2	PLACEBO	44	38	22	29
3	3	100 MG BUSPIRONE	44	75	190	74
3	4	50 MG BUSPIRONE	12	33	13	11
3	5	200 MG SULPIRIDE	21	310	110	78
4	1	50 MG BUSPIRONE	17	45	14	12
4	2	100 MG BUSPIRONE	14	94	32	13
4	3	200 MG SULPIRIDE	13	105	45	31
4	4	25 MG BUSPIRONE	29	38	35	27
4	5	PLACEBO	40	26	31	34
5	1	PLACEBO	12	10	9	10
5	2	200 MG SULPIRIDE	27	240	130	84
5	3	25 MG BUSPIRONE	9	8	31	12
5	4	100 MG BUSPIRONE	17	70	27	15
5	5	50 MG BUSPIRONE	42	55	73	37
6	1	PLACEBO	12	9	10	10
6	2	25 MG BUSPIRONE	13	15	15	12
6	3	200 MG SULPIRIDE	17	98	55	38
6	4	50 MG BUSPIRONE	16	49	15	12
6	5	100 MG BUSPIRONE	11	64	24	18
7	1	25 MG BUSPIRONE	27	33	37	31
7	2	PLACEBO	62	37	34	34
7	3	100 MG BUSPIRONE	53	77	150	78
7	4	200 MG SULPIRIDE	45	390	225	150
7	5	50 MG BUSPIRONE	51	39	66	41
8	1	200 MG SULPIRIDE	14	93	69	39
8	2	50 MG BUSPIRONE	19	19	26	15
8	3	PLACEBO	15	13	19	14
8	4	100 MG BUSPIRONE	19	97	33	22
8	5	25 MG BUSPIRONE	22	16	14	14
9	1	50 MG BUSPIRONE	19	43	15	12
9	2	100 MG BUSPIRONE	15	105	39	14
9	3	25 MG BUSPIRONE	12	37	14	8
9	4	PLACEBO	18	12	14	13
9	5	200 MG SULPIRIDE	22	300	120	74
10	1	100 MG BUSPIRONE	25	23	78	56
10	2	200 MG SULPIRIDE	32	250	135	82
10	3	50 MG BUSPIRONE	36	31	50	41
10	4	25 MG BUSPIRONE	30	38	38	33
10	5	PLACEBO	38	34	34	32

APPENDIX VIII

Types of Adverse Reactions in Those Patients Discontinuing Due to Side Effects
(in Descending Order of Buspirone Incidence)

Adverse Reaction*	Number (%) of Dropouts			
	Buspirone (n=57)	Diazepam (n=22)	Clorazepate (n=9)	Placebo (n=5)
Dizziness	7 (12%)	0	1 (11%)	0
Insomnia	7 (12%)	1 (5%)	0	0
Headache	6 (11%)	0	0	0
Drowsiness	5 (9%)	6 (27%)	2 (22%)	1 (20%)
Fatigue/Weakness	5 (9%)	2 (9%)	0	0
Nervousness/Restlessness	4 (7%)	0	0	0
Confusion	3 (5%)	2 (9%)	0	0
Excitement	3 (5%)	0	1 (11%)	0
Abdominal Pain	2 (4%)	1 (5%)	0	0
Diarrhea	2 (4%)	0	0	0
Pruritus	2 (4%)	1 (5%)	0	0
Blurred Vision	1 (2%)	0	0	0
Decreased Concentration	1 (2%)	1 (5%)	0	0
Enuresis	1 (2%)	0	0	0
Hyperphagia	1 (2%)	0	0	0
Lightheadedness	1 (2%)	1 (5%)	0	0
Nausea/Vomiting	1 (2%)	2 (9%)	0	2 (40%)
Nightmares/Vivid Dreams	1 (2%)	1 (5%)	1 (11%)	0
Numbness	1 (2%)	0	0	0
Palpitations	1 (2%)	0	0	0
Paresthesia	1 (2%)	0	0	1 (20%)
Syncope	1 (2%)	0	0	0
Incoordination	0	2 (9%)	0	0
Hypotension	0	1 (5%)	0	0
Skin Rash	0	1 (5%)	0	0
Depression	0	0	4 (44%)	0
Dry Mouth	0	0	0	1 (20%)

n = number of patients who dropped out during Part I due to side effects

*Most patients who discontinued because of side effects had multiple side effects. The side effect chosen was usually either the most severe or the one that the investigator considered to be drug related.

Appendix IX

Number of Patients	Treatment Emergent Symptom Incidence			
	Buspirone (n=748	Placebo (n=245)	Diazepam (n=325)	Clorazepate (n=81)
	% of Patients Reporting:			
Cardiovascular				
Tachycardia/Palpitations	1.3	2.5	0.6	0.0
CHest Pain	1.2	1.6	0.6	0.0
CNS				
Drowsiness	8.6	10.2	32.0	25.9
Nervousness	4.3	1.2	1.5	2.5
Insomnia	4.1	2.0	3.1	2.5
Depression	2.5	2.5	8.0	9.9
Excitement	2.1	0.8	0.9	4.9
Decreased Concentration	2.0	1.6	2.5	0.0
Nightmares/Vivid Dreams	1.9	0.8	2.2	2.5
Anger/Hostility	1.1	1.2	2.5	0.0
Confusion	1.1	1.2	2.5	0.0
EENT				
Blurred Vision	1.2	1.2	2.5	0.0
Gastrointestinal				
Nausea	5.7	4.5	3.1	0.0
Diarrhea	2.8	0.8	0.6	3.7
Abdominal/Gastric Distress	2.3	1.6	1.5	0.0
Dry Mouth	2.3	4.1	4.0	2.5
Constipation	1.3	0.8	1.2	0.0
Neurological				
Dizziness	8.6	2.9	6.8	6.2
Lightheadiness	2.4	1.2	2.5	0.0
Paresthesia	2.0	0.4	0.3	0.0
Incoordination	1.7	0.8	2.5	1.2
Skin				
Skin Rash	1.2	0.8	1.2	1.2
Flushing	1.1	0.0	0.3	0.0
Miscellaneous				
Headache	7.9	2.0	6.5	2.5
Fatigue	4.4	4.9	12.6	9.9
Weakness	2.4	1.2	6.5	2.5
Sweating/Clamminess	1.3	0.0	1.2	0.0

APPENDIX X

CONTROLLED CLINICAL STUDIES - SAFETY

Incidence[a] of Adverse Reactions by Treatment by Investigator
11-Study Composite

Treatment: Buspirone

Protocol	B vs B vs P					B vs C				B vs B				
Study Number	764	994	995	996	1012	Protocol Total	1029	1032	1041	Protocol Total	1000 - 1048	1049	Protocol Total	Overall Treatment Total
Number of Patients	n=20	n=81	n=64	n=48	n=13	n=246	n=186	n=50	n=99	n=255	n=105	n=51	n=85	n=746
Number (%) Pts. Reporting														
Body System Primary Term														
CARDIOVASCULAR														
Chest Pain	0	1 (1%)	2 (3%)	0	0	3 (1%)	1 (1%)	2 (4%)	1 (1%)	4 (2%)	1 (1%)	1 (2%)	0	2 (1%)	9 (1%)
Hypotension	0	1 (1%)	0	0	0	1(<1%)	0	0	0	0	1 (1%)	0	0	1(<1%)	2(<1%)
Syncope	0	1 (1%)	0	0	0	1(<1%)	1 (1%)	0	2 (2%)	3 (1%)	0	0	0	0	4(<1%)
Tachycard./Palpitations	0	1 (1%)	0	0	1 (2%)	2(<1%)	3 (3%)	0	1 (1%)	4 (2%)	2 (2%)	1 (2%)	1 (1%)	4 (2%)	10 (1%)
TOTAL	0	4 (5%)	2 (3%)	0	1 (2%)	7 (3%)	4 (4%)	2 (4%)	4 (4%)	10 (4%)	3 (3%)	2 (4%)	1 (1%)	6 (2%)	23 (3%)
CENTRAL NERVOUS SYSTEM															
Anger/Hostility	0	1 (1%)	0	1 (2%)	3 (7%)	5 (2%)	0	0	2 (2%)	2(<1%)	1 (1%)	0	0	1(<1%)	8 (1%)
Claustrophobic Feeling	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Confusion	0	1 (1%)	1 (2%)	0	1 (2%)	3 (1%)	0	2 (4%)	0	2(<1%)	2 (2%)	1 (2%)	0	3 (1%)	8 (1%)
Decrease Concentration	0	1 (1%)	1 (2%)	2 (5%)	0	4 (2%)	0	0	8 (8%)	8 (3%)	0	1 (2%)	2 (2%)	3 (1%)	15 (2%)
Depersonalization	0	1 (1%)	0	0	1 (2%)	2(<1%)	0	0	0	0	0	0	0	0	2(<1%)
Depression	0	1 (1%)	0	5(13%)	0	6 (2%)	1 (1%)	2 (4%)	6 (6%)	9 (4%)	4 (4%)	0	0	4 (2%)	19 (3%)
Drowsiness	0	10(22%)	2 (3%)	1 (2%)	6(14%)	27(11%)	1 (1%)	5(10%)	19(19%)	25(10%)	4 (4%)	7(14%)	1 (1%)	12 (5%)	64 (9%)
Dysphoria	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Euphoria	0	0	0	1 (2%)	0	1(<1%)	0	0	0	0	0	0	0	0	1(<1%)
Excitement	0	1 (1%)	0	4(10%)	0	5 (2%)	0	0	0	0	0	0	0	3 (1%)	16 (2%)
Insomnia	0	5 (6%)	0	2 (5%)	0	7 (3%)	1 (1%)	0	8 (8%)	8 (3%)	0	0	0	0	15 (2%)
Nervousness	0	4 (5%)	0	11(27%)	1 (2%)	16 (6%)	2 (2%)	1 (2%)	9 (9%)	10 (4%)	2 (2%)	1 (2%)	0	3 (1%)	31 (4%)
Nightmare/Vivid Dreams	0	0	0	1 (2%)	0	1(<1%)	0	0	5 (5%)	8 (3%)	2 (2%)	4 (8%)	3 (3%)	14 (6%)	32 (4%)
Suicidal Thoughts	0	0	0	0	0	0	0	0	11(11%)	11 (4%)	2 (2%)	0	2 (2%)	8 (3%)	32 (4%)
TOTAL	0	26(32%)	4 (6%)	14(35%)	8(19%)	52(21%)	4 (4%)	9(18%)	46(45%)	59(23%)	16(15%)	13(25%)	6 (7%)	35(14%)	146(20%)
EENT															
Blurred Vision	0	2 (2%)	0	2 (5%)	2 (5%)	6 (2%)	0	0	2 (2%)	2(<1%)	1 (1%)	0	0	1(<1%)	9 (1%)
Conjunctivitis	0	0	0	0	0	0	0	1 (2%)	0	1(<1%)	0	0	1 (1%)	1(<1%)	2(<1%)
Dimness of Vision	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eyes Red/Tired/Itching	0	0	0	1 (2%)	0	1(<1%)	0	0	1 (1%)	1(<1%)	0	0	0	0	2(<1%)
Pressure on Eyes	0	0	0	0	0	0	0	0	0	0	0	1 (2%)	0	1(<1%)	1(<1%)
Tinnitus	0	0	0	0	1 (2%)	1(<1%)	0	0	1 (1%)	1(<1%)	0	2 (4%)	1 (1%)	3 (1%)	5(<1%)
Unusual Sense-Smell	0	0	0	0	0	0	0	0	0	0	0	1 (2%)	0	1(<1%)	1(<1%)
TOTAL	0	2 (2%)	0	2 (5%)	3 (7%)	7 (3%)	0	1 (2%)	4 (4%)	5 (2%)	1 (1%)	4 (8%)	2 (2%)	7 (3%)	19 (3%)

Treatment Emphysema

Protocol	764	994	995	996	1012	Protocol Total	1029	1032	1041	Protocol Total	1008	1046	1049	Protocol Total	Overall Treatment Total
Study Number															
Number of Patients	n=20	n=81	n=64	n=40	n=43	n=248	n=106	n=50	n=99	n=255	n=105	n=51	n=89	n=245	n=748
Number (%) Ptas. Reporting															
Body System Primary Term															
GASTROINTESTINAL															
Abdom./Gastric Distress	0	3 (4%)	0	1 (2%)	1 (2%)	5 (2%)	1 (1%)	2 (4%)	2 (2%)	5 (2%)	2 (2%)	4 (8%)	1 (1%)	7 (3%)	17 (2%)
Anorexia	0	1 (1%)	1 (2%)	0	0	2(<1%)	0	0	0	0	0	0	0	0	2(<1%)
Constipation	0	2 (2%)	0	0	0	2(<1%)	0	1 (2%)	3 (3%)	4 (2%)	1 (1%)	2 (4%)	1 (1%)	4 (2%)	10 (1%)
Diarrhea	0	2 (2%)	0	1 (2%)	0	3 (1%)	2 (2%)	1 (2%)	9 (9%)	12 (5%)	3 (3%)	2 (4%)	1 (1%)	6 (2%)	21 (3%)
Dry Mouth	0	2 (2%)	0	2 (5%)	1 (2%)	5 (2%)	0	0	7 (7%)	7 (3%)	1 (1%)	3 (6%)	1 (1%)	5 (2%)	17 (2%)
Flatulence	0	0	0	1 (2%)	0	1(<1%)	0	0	1 (1%)	1(<1%)	0	1 (2%)	1 (1%)	2 (1%)	4(<1%)
Hypersalivation	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	0	0	1(<1%)
Increased Appetite	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	1 (2%)	2 (2%)	3 (1%)	4(<1%)
Nausea	0	4 (5%)	3 (5%)	4(10%)	3 (7%)	14 (6%)	1 (1%)	2 (4%)	15(15%)	18 (7%)	6 (6%)	2 (4%)	3 (3%)	11 (4%)	43 (6%)
Tongue-Burning	0	0	0	1 (2%)	0	1(<1%)	0	0	0	0	0	0	0	0	1(<1%)
Vomiting	0	0	0	1 (2%)	0	1(<1%)	0	0	2 (2%)	2(<1%)	3 (3%)	0	1 (1%)	4 (2%)	7(<1%)
TOTAL	0	8(10%)	3 (5%)	9(22%)	5(12%)	25(10%)	3 (3%)	5(10%)	29(29%)	37(15%)	9 (9%)	12(24%)	11(12%)	32(13%)	94(13%)
GENITOURINARY															
Amenorrhea	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	0	0	1(<1%)
Delayed Urine Flow	0	1 (1%)	0	0	0	1(<1%)	0	0	0	0	0	0	0	0	1(<1%)
Enuresis	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0	1(<1%)	1(<1%)
Nocturia	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	0	0	1(<1%)
Urinary Bleeding	0	1 (1%)	0	0	0	1(<1%)	0	1 (2%)	0	1(<1%)	0	0	0	0	2(<1%)
Urinary Frequency	0	0	0	0	0	0	0	0	0	0	0	1 (2%)	0	1(<1%)	1(<1%)
TOTAL	0	1 (1%)	0	0	0	1(<1%)	0	1 (2%)	2 (2%)	3 (1%)	1 (1%)	1 (2%)	0	2 (1%)	6(<1%)
MUSCULOSKELETAL															
Arthralgias	0	0	0	0	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	1(<1%)
Muscle Cramps	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Muscle Spasms	0	0	0	1 (2%)	1 (2%)	2(<1%)	0	0	1 (1%)	1(<1%)	0	0	1 (1%)	1(<1%)	4(<1%)
Muscule. Aches/Pains	0	1 (1%)	0	1 (2%)	0	2(<1%)	0	0	0	0	0	1 (2%)	0	1(<1%)	3(<1%)
Rigid/Stiff Muscles	0	1 (1%)	0	0	0	1(<1%)	1 (1%)	0	0	1(<1%)	2 (2%)	0	0	2 (1%)	4(<1%)
TOTAL	0	1 (1%)	0	2 (5%)	1 (2%)	4 (2%)	1 (1%)	0	1 (1%)	2(<1%)	2 (2%)	1 (2%)	2 (2%)	5 (2%)	11 (1%)

Treatment: Buspirone

Incidence* of Adverse Reactions by Treatment by Investigator
11-Study Composite

Protocol	B vs D vs P						B vs C				B vs D				
Study Number	764	994	995	996	1012	Protocol Total	1029	1032	1041	Protocol Total	1000	1048	1049	Protocol Total	Overall Treatment Total
Number of Patients	n=20	n=81	n=64	n=48	n=43	n=248	n=106	n=50	n=99	n=255	n=105	n=51	n=89	n=245	n=748
Number (%) Pts. Reporting															
Body System Primary Term															
NEUROLOGICAL															
Decrease Reaction Time	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	0	0	1(<1%)
Dizziness	3(15%)	10(12%)	2 (3%)	4(10%)	3 (7%)	22 (9%)	6 (5%)	6(12%)	16(16%)	28(11%)	4 (4%)	7(14%)	3 (3%)	14 (6%)	64 (9%)
Incoordination	0	1 (1%)	0	1 (2%)	1 (2%)	3 (1%)	1 (1%)	3 (6%)	3 (3%)	7 (3%)	1 (1%)	1 (2%)	1 (1%)	3 (1%)	13 (2%)
Involuntary Movement	0	1 (1%)	0	0	0	1(<1%)	0	0	1 (1%)	1(<1%)	0	0	0	0	2(<1%)
Lightheadedness	3(15%)	1 (1%)	1 (2%)	1 (1%)	2 (5%)	8 (3%)	2 (2%)	0	4 (4%)	6 (2%)	1 (1%)	2 (4%)	1 (1%)	4 (2%)	18 (2%)
Numbness	0	2 (2%)	1 (2%)	0	0	3 (1%)	1 (1%)	0	0	1(<1%)	0	1 (2%)	0	1(<1%)	5(<1%)
Paresthesia	0	0	2 (3%)	3 (7%)	0	5 (2%)	0	4 (8%)	2 (2%)	6 (2%)	1 (1%)	1 (2%)	2 (2%)	4 (2%)	15 (2%)
Slurred Speech	0	0	0	0	0	0	0	1 (2%)	0	1(<1%)	0	0	0	0	1(<1%)
Stupor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tremor	0	1 (1%)	0	0	0	1(<1%)	0	0	0	0	0	0	1 (1%)	1(<1%)	2(<1%)
TOTAL	3(15%)	14(17%)	5 (8%)	8(20%)	5(12%)	35(14%)	9 (8%)	9(18%)	24(24%)	42(16%)	6 (6%)	9(18%)	7 (8%)	22 (9%)	99(13%)
RESPIRATORY															
Nasal Congestion	0	0	0	0	0	0	1 (1%)	1 (2%)	2 (2%)	4 (2%)	0	0	0	0	4(<1%)
Shortness of Breath	0	0	0	0	0	0	0	0	2 (2%)	2(<1%)	0	0	0	0	2(<1%)
TOTAL	0	0	0	0	0	0	1 (1%)	1 (2%)	4 (4%)	6 (2%)	0	0	0	0	6(<1%)
SEXUAL FUNCTION															
Decreased Libido	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	0	0	1(<1%)
Increased Libido	0	0	0	0	0	0	0	0	2 (2%)	2(<1%)	0	0	0	0	2(<1%)
TOTAL	0	0	0	0	0	0	0	0	3 (3%)	3 (1%)	0	0	0	0	3(<1%)
SKIN															
Acne	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Blisters	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0	1(<1%)	1(<1%)
Bruises Easily	0	0	0	0	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	1(<1%)
Edema	0	0	0	0	0	0	0	0	0	0	0	2 (4%)	0	2 (1%)	2(<1%)
Facial Edema	0	0	0	1 (2%)	0	1(<1%)	0	1 (2%)	0	1(<1%)	0	0	1 (1%)	1(<1%)	3(<1%)
Flushing	0	1 (1%)	0	0	0	1(<1%)	0	1 (2%)	3 (3%)	4 (2%)	1 (1%)	1 (2%)	1 (1%)	3 (1%)	8 (1%)
Pruritus	0	1 (1%)	0	1 (2%)	1 (2%)	3 (1%)	0	0	1 (1%)	1(<1%)	1 (1%)	0	2 (2%)	3 (1%)	7(<1%)
Skin Rash	0	1 (1%)	0	3 (7%)	0	4 (2%)	0	0	1 (1%)	1(<1%)	2 (2%)	0	2 (2%)	4 (2%)	9 (1%)
TOTAL	0	3 (4%)	0	5(13%)	1 (2%)	9 (4%)	0	2 (4%)	5 (5%)	7 (3%)	4 (4%)	3 (6%)	6 (7%)	13 (5%)	29 (4%)

CONTROLLED CLINICAL STUDIES - SAFETY

Incidence* of Adverse Reactions by Treatment by Investigator
11-Study Composite

Treatment: Buspirone

Protocol	B vs B vs P						B vs C				B vs D				
Study Number	764	994	995	996	1012	Protocol Total	1029	1032	1041	Protocol Total	1008	1048	1049	Protocol Total	Overall Treatment Total
Number of Patients	n=20	n=61	n=64	n=48	n=43	n=248	n=106	n=50	n=99	n=255	n=105	n=51	n=89	n=245	n=748
Number (%) Ptns. Reporting															
Body System Primary Term															
MISCELLANEOUS															
Alcohol Abuse	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0	1(<1%)	1(<1%)
Fatigue	0	3 (4%)	1 (2%)	2 (5%)	3 (7%)	9 (4%)	2 (2%)	3 (6%)	9 (9%)	14 (5%)	3 (3%)	5(10%)	2 (2%)	10 (4%)	33 (4%)
Fever	0	0	0	0	0	0	1 (1%)	0	0	1(<1%)	0	0	1 (1%)	1(<1%)	2(<1%)
Headache	0	8(10%)	1 (2%)	4(10%)	3 (7%)	16 (6%)	3 (3%)	1 (2%)	19(19%)	23 (9%)	3 (3%)	7(14%)	10(11%)	20 (8%)	59 (8%)
Sore Throat	0	0	0	0	0	0	0	0	1 (1%)	1(<1%)	0	0	1 (1%)	1(<1%)	2(<1%)
Sweating/Clamminess	1 (5%)	1 (1%)	0	0	0	2(<1%)	0	1 (2%)	5 (5%)	6 (2%)	1 (1%)	0	1 (1%)	2 (1%)	10 (1%)
Voice Loss	0	0	0	0	1 (2%)	1(<1%)	0	0	0	0	0	0	0	0	1(<1%)
Weakness	2(10%)	4 (5%)	0	0	0	6 (2%)	1 (1%)	1 (2%)	8 (8%)	10 (4%)	0	2 (4%)	0	2 (1%)	18 (2%)
Weight Gain	0	0	0	0	1 (2%)	1(<1%)	0	1 (2%)	0	1(<1%)	0	0	0	0	2(<1%)
TOTAL	2(10%)	13(16%)	2 (3%)	5(13%)	7(16%)	29(12%)	6 (6%)	7(14%)	35(35%)	48(19%)	8 (8%)	12(24%)	13(15%)	33(13%)	110(15%)

*Incidences based on adverse reactions reported by all entered patients during the initial 4-week study period.

APPENDIX XI

Incidence of Adverse Reactions Reported by Buspirone-Treated Patients (Compared with Diazepam- and Placebo-Treated Patients) Entered in Clinical Studies Conducted Outside the U.S.

(9-Study Composite)

Adverse Reaction	Treatment* Buspirone (n=182)	Diazepam (n=124)	Placebo (n=93)
Dizziness	20 (11%)	5 (4%)	1 (1%)
Headache	18 (10%)	4 (3%)	6 (6%)
Nausea	10 (5%)	2 (2%)	0
Lethargy	9 (5%)	10 (8%)	1 (1%)
Stomach Problems	7 (4%)	2 (2%)	4 (4%)
Insomnia	5 (3%)	1 (<1%)	1 (1%)
Agitation/Stimulation	4 (2%)	1 (<1%)	0
Tremors	4 (2%)	1 (<1%)	0
Clammy/Sweaty	3 (2%)	0	1 (1%)
Excitement	3 (2%)	1 (<1%)	0
Flushing/Warm	3 (2%)	1 (<1%)	2 (2%)
Nervousness	3 (2%)	4 (3%)	3 (3%)
Noise/Light Irritation	3 (2%)	1 (<1%)	1 (1%)
Abdominal/Gastric Distress	2 (1%)	1 (<1%)	1 (1%)
Depression	2 (1%)	2 (2%)	0
Diarrhea	2 (1%)	1 (<1%)	1 (1%)
Lightheadedness	2 (1%)	0	0
Muscle Spasms	2 (1%)	2 (2%)	0
Palpitations	2 (1%)	1 (<1%)	0
Paresthesia	2 (1%)	2 (2%)	1 (1%)
Photosensitivity	2 (1%)	0	0
Claustrophobia	1 (<1%)	0	0
Concentration Loss	1 (<1%)	0	0
Constipation	1 (<1%)	2 (2%)	0
Depersonalization	1 (<1%)	1 (<1%)	0
Dry Mouth	1 (<1%)	0	1 (1%)
Eye Pain	1 (<1%)	0	0
Faintness	1 (<1%)	1 (<1%)	0
Fear	1 (<1%)	2 (2%)	1 (1%)
Hallucinations	1 (<1%)	1 (<1%)	0
Intoxication Symptoms	1 (<1%)	2 (2%)	1 (1%)
Menstrual Irregularities	1 (<1%)	0	0
Muscle Pain	1 (<1%)	1 (<1%)	0
Perceptual Changes	1 (<1%)	2 (2%)	1 (1%)
Upper Airway Infections/Inflammation	1 (<1%)	0	0
Vomiting	1 (<1%)	3 (2%)	0
Weight Loss	1 (<1%)	0	0

*Treatment n's may include the same subject multiple times if he/she reported adverse reactions after crossover to an alternate treatment.

APPENDIX XII

CONTROLLED CLINICAL STUDIES - SAFETY

Incidence Summary of Normal-to-Abnormal[a] Lab Test Variations by Treatment for Combined Protocols

11-Study Composite
(Studies #764, 994, 995, 996, 1008, 1012, 1029, 1032, 1041, 1048, 1049)

Lab Test Indicator	Buspirone n	Buspirone N-AL	Buspirone N-AH	Diazepam n	Diazepam N-AL	Diazepam N-AH	Clorazepate n	Clorazepate N-AL	Clorazepate N-AH	Placebo n	Placebo N-AL	Placebo N-AH	Significance (p-values)[aa] B vs B CHH	B vs B FISH	B vs C CHH	B vs C FISH	B vs P CHH	B vs P FISH
CBC																		
Hematocrit	426	18 (4%)	1(<1%)	190	7 (4%)	1(<1%)	54	5 (9%)	0	114	7 (6%)	0	1.00	1.00	.09 B	.17	.65	.46
Hemoglobin	426	2(<1%)	2(<1%)	190	2 (1%)	0	54	0	0	114	2 (2%)	0	.36	1.00	.45	1.00	.16	.61
RBC	426	8 (2%)	2(<1%)	190	4 (2%)	0	55	0	0	114	7 (6%)	0	.64	1.00	1.00	.61	.86 B	.06 B
MCV	417	4 (1%)	9 (2%)	174	2 (1%)	6 (3%)	55	0	0	104	1 (1%)	1 (1%)	.38	.46	.56	.38	.16	.75
MCH	415	0	7 (2%)	173	1(<1%)	6 (3%)	55	0	0	103	2 (2%)	4 (4%)	.20	.13	.21	1.00	.51	.03 B
MCHC	414	20 (5%)	10 (2%)	173	10 (6%)	4 (2%)	55	2 (4%)	1 (2%)	103	6 (6%)	3 (3%)	.76	.73	1.00	.78	.90	.68
WBC	425	14 (3%)	13 (3%)	188	8 (4%)	6 (3%)	55	3 (5%)	4 (7%)	114	3 (3%)	4 (4%)	.15	.60	.79	.09 B	.33	1.00
Neutrophils	441	38 (9%)	34 (8%)	178	18(10%)	10 (6%)	24	2 (4%)	3 (6%)	100	7 (6%)	8 (7%)	.08 B	.72	.83	.23	1.00	.47
Bands, Differential	225	0	2(<1%)	74	0	4 (5%)	34	0	4(12%)	30	0	0	.001 B	.04 B	<.001 B	<.01 B	.43	1.00
Lymphocytes	414	35 (8%)	34 (8%)	178	11 (6%)	22(12%)	52	4 (8%)	6(12%)	100	9 (8%)	6 (6%)	.82 B	.64	.61	.71	1.00	.56
Monocytes	406	1(<1%)	20 (5%)	172	9 (5%)	9 (5%)	52	0	1 (2%)	103	1 (1%)	4 (4%)	.86 B	.83 B	.27	.49	.72	1.00
Eosinophils	406	2(<1%)	15 (4%)	173	3 (2%)	8 (5%)	52	0	1 (2%)	99	0	5 (5%)	.75	.22	.44	.71	1.00	.78
Basophils (Percent)	393	0	14 (4%)	155	0	6 (4%)	52	0	4 (8%)	86	0	0	.65	.01	.19	.15	.04 P	.09 P
Platelet Est.	239	0	0	86	0	2 (2%)	30	0	0	.44	0	0	.05†	.07 B	.56	1.00	1.00	1.00
Blood Chemistry																		
BUN	441	2(<1%)	5 (1%)	195	1(<1%)	3 (2%)	58	0	2 (3%)	113	2 (2%)	1(<1%)	1.00	.74	.28	.28	.81	.43
Creatinine, Serum	435	0	4(<1%)	188	0	0	56	0	1 (2%)	106	2 (2%)	3 (3%)	.20	.33	.55	.46	1.00	.02 B
BUN/Creatinine Ratio	3	0	0	6	0	0	0	--	--	4	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Uric Acid	434	14 (3%)	10 (2%)	188	5 (3%)	4 (2%)	58	2 (3%)	0	106	2 (2%)	0	.80	1.00	.31	.76	1.00	.14
Glucose	438	15 (3%)	18 (4%)	181	0	9 (5%)	57	3 (5%)	4 (7%)	107	5 (5%)	2 (2%)	.15	.29	.26	.20	.34	.44
Total Protein	433	2(<1%)	7 (2%)	180	0	2 (1%)	58	0	0	106	0	1(<1%)	.65	.52	.43	.61	.55	.70
Albumin	429	0	2(<1%)	179	0	0	57	0	1 (2%)	106	0	1(<1%)	.40	1.00	.23	.31	.68	.49
Globulin	418	15 (4%)	1(<1%)	173	4 (2%)	0	55	3 (5%)	0	95	4 (4%)	0	.86	.46	.71	.48	.64	.77
Albumin Globulin Ratio	416	4 (1%)	6 (1%)	171	2 (1%)	3 (2%)	55	0	0	91	2 (2%)	1 (1%)	1.00	.78	.68	.62	.28	.71
% Transferrin Sat.	2	0	0	1	0	0	0	--	--	2	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Total Bilirubin	430	2(<1%)	5 (1%)	188	0	0	58	0	0	105	1 (1%)	1 (1%)	.63	.11	.68	1.00	.40	.69
Bilirubin, Direct	399	0	3(<1%)	155	0	1(<1%)	54	0	0	84	0	1 (1%)	.89	1.00	.52	1.00	.69	.54
Bilirubin, Indirect	5	0	0	4	0	0	0	--	--	7	0	0	1.00	1.00	1.00	1.00	1.00	1.00
SGOT	437	0	12 (3%)	188	0	1(<1%)	58	0	0	112	0	1(<1%)	.38	.12	.19	.38	.90	.48
SGPT	411	1(<1%)	16 (4%)	167	0	1(<1%)	56	0	1 (2%)	91	0	2 (2%)	.47	.03 B	.19	.71	1.00	.55
LDH	425	0	6 (1%)	175	0	4 (2%)	58	0	2 (3%)	105	0	4 (4%)	.17	.49	.10 B	.25	.06 B	.12
Alkaline Phosphatase	441	2(<1%)	2(<1%)	194	1(<1%)	6 (3%)	58	0	3 (5%)	114	3 (3%)	4 (4%)	.01 B	.04 B	.01†	.04 B	.27	.002 B

[a] Normal-to-Abnormal Variations: N-AL = Normal or above normal at baseline/below normal range at endpoint of Part I.
N-AH = Normal or below normal at baseline/above normal range at endpoint of Part I.

[aa] Letter following statistically significant p-value indicates which treatment was favored in the analysis.

†The p-value from the CHH analysis is probably invalid because the response distribution is degenerate in the sense of being concentrated in a single response category.

CONTROLLED CLINICAL STUDIES - SAFETY
(continued)

Incidence Summary of Normal-to-Abnormal[A] Lab Test Variations by Treatment for Combined Protocols

11-Study Composite
(Studies #764, 994, 995, 996, 1080, 1012, 1029, 1032, 1041, 1048, 1049)

Lab Test Indicator	Buspirone n	Buspirone N-AL	Buspirone N-AH	Diazepam n	Diazepam N-AL	Diazepam N-AH	Clorazepate n	Clorazepate N-AL	Clorazepate N-AH	Placebo n	Placebo N-AL	Placebo N-AH	Significance (p-values)[AA] B vs D CMH	B vs D FISH	B vs C CMH	B vs C FISH	B vs P CMH	B vs P FISH
Blood Chemistry (cont.)																		
GGTP	399	0	8 (2%)	151	0	4 (3%)	55	0	0	80	0	0	1.00	.74	.64	.60	1.00	.36
Sodium, Serum	423	16 (4%)	3(<1%)	176	4 (2%)	1(<1%)	57	3 (5%)	1 (2%)	97	4 (4%)	0	.39	.49	.51	.34	.74	1.00
Potassium, Serum	388	4 (1%)	6 (2%)	170	4 (2%)	5 (3%)	51	1 (2%)	1 (2%)	97	2 (2%)	3 (3%)	.69	.13	1.00	.64	.40	.20
Chloride	418	9 (2%)	6 (1%)	169	2 (1%)	2 (1%)	55	0	2 (4%)	95	4 (4%)	4 (4%)	.76	.61	.07 B	1.00	.59	.05 B
CO_2, Serum	6	0	0	9	0	0	0	--	--	8	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Calcium	428	1(<1%)	3(<1%)	175	2 (1%)	0	57	0	0	104	1 (1%)	0	.22	1.00	.72	1.00	.18	1.00
Magnesium, Serum	151	1(<1%)	0	65	0	0	13	0	0	45	0	2 (4%)	.51	1.00	.77	1.00	.01†	.13
Phosphorus (mg/dl)	422	0	6 (1%)	178	0	0	57	0	0	106	0	2 (2%)	.11	.19	.36	1.00	.36	.66
Iron, Serum	387	16 (4%)	7 (2%)	150	6 (4%)	3 (2%)	54	4 (7%)	1 (2%)	81	2 (2%)	2 (2%)	1.00	1.00	.02 B	.37	.63	1.00
Cholesterol	437	2(<1%)	4(<1%)	180	1(<1%)	4 (2%)	58	1 (2%)	1 (2%)	106	1(<1%)	3 (3%)	.06 B	.31	.71	.24	.02 B	.11
Triglycerides	419	0	52(12%)	172	1(<1%)	13 (8%)	56	0	5 (9%)	96	0	8 (8%)	.18	.15	.64	.66	.103	.30
T_4 Thyroid Test	0	--	--	1	0	0	0	--	--	0	--	--	1.00	1.00	1.00	1.00	1.00	1.00
TIBC	5	0	0	3	0	0	0	--	--	2	0	0	1.00	1.00	1.00	1.00	1.00	1.00
UIBC	2	0	0	1	0	0	0	--	--	2	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Urinalysis																		
Acetone, Urine	408	0	7 (2%)	148	0	4 (3%)	51	0	2 (4%)	85	0	2 (2%)	.23	.49	.28	.26	.69	.66
Bile, Urine	9	0	0	4	0	0	0	--	--	7	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Bilirubin, Urine	4	0	0	6	0	0	0	--	--	8	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Blood, Urine	395	6	16 (4%)	137	0	6 (4%)	51	0	5(10%)	80	0	7 (9%)	.81	.81	.11	.79	.24	.09 B
Casts	180	0	1(<1%)	76	0	0	16	0	0	51	0	0	.52	1.00	.77	1.00	.60	1.00
Casts, Amount	334	0	9 (3%)	114	0	4 (4%)	46	0	2 (4%)	60	0	0	.77	.75	.62	.63	.18	.37
Ketones, Urine	7	0	0	8	0	0	0	--	--	12	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Nitrite	3	0	0	4	0	0	0	--	--	7	0	0	1.00	1.00	1.00	1.00	1.00	1.00
Occult Blood, Urine	13	0	1 (8%)	14	0	1 (7%)	0	--	--	13	0	0	1.00	1.00	1.00	1.00	.32	1.00
pH	11	0	0	16	0	1 (6%)	0	--	--	13	0	0	.41	1.00	1.00	1.00	1.00	1.00
Protein	426	0	11 (3%)	172	0	5 (3%)	51	0	2 (4%)	110	0	4 (4%)	.76	.79	.60	.64	.22	.52
RBC/HPF	404	0	12 (3%)	158	0	3 (2%)	51	0	1 (2%)	90	0	3 (3%)	.26	.57	.77	1.00	.91	.74
Specific Gravity	214	22(10%)	14 (7%)	59	7(12%)	0	38	7(18%)	2 (5%)	29	0	2 (7%)	.38	.42	.32	.36	.14	.27
Sugar	427	0	7 (2%)	172	0	0	51	0	1 (2%)	109	0	0	.04 B	.20	.48	.60	.15	.35
Urobilinogen	3	0	0	4	0	1(25%)	0	--	--	8	0	1(13%)	.39	1.00	1.00	1.00	.51	1.00
WBC/HPF	412	0	14 (3%)	162	0	10 (6%)	50	0	3 (6%)	95	0	7 (7%)	.21	.16	.54	.41	.23	.09 B

[A] Normal-to-Abnormal Variations: N-AL = Normal or above normal baseline/below normal range at endpoint of Part 1.
N-AH = Normal or below normal baseline/above normal range at endpoint of Part 1.

[AA] Letter following statistically significant p-value indicates which treatment was favored in the analysis.

†The p-value from the CMH analysis is probably invalid because the response distribution is degenerate in the sense of being concentrated in a single response category.

CONTROLLED CLINICAL STUDIES - SAFETY

Incidence of EKG Abnormalities* by Treatment, Investigator and Protocol

11-Study Composite

Study #	Quazipone n	Quazipone N-A	Quazipone A-A	Quazipone A-N	Diazepam n	Diazepam N-A	Diazepam A-A	Diazepam A-N	Clorazepate n	Clorazepate N-A	Clorazepate A-A	Clorazepate A-N	Placebo n	Placebo N-A	Placebo A-A	Placebo A-N	Significance (p-value)** Q vs D (300)	Q vs D (150)	Q vs C (300)	Q vs C (150)	Q vs P (300)	Q vs P (150)
7601	1	0	0	0	0	0	0	0					1	0	0	0						
990	43	2 (5%)	1 (2%)	2 (5%)	46	0	1 (2%)	0					44	0	2 (7%)	0						
995	34	0	5 (15%)	1 (3%)	38	1 (3%)	4 (11%)	1 (3%)					35	4 (11%)	6 (17%)	1 (3%)						
996	35	1 (3%)	3 (9%)	3 (9%)	23	0	5 (16%)	2 (6%)					33	1 (3%)	2 (6%)	0						
1012	32	0	3 (9%)	0	30	0	0	0					40	1 (3%)	3 (3%)	0						
Protocol Total	150	3 (2%)	12 (8%)	6 (4%)	156	1 (<1%)	10 (6%)	3 (2%)					153	6 (4%)	12 (8%)	1 (<1%)	.05	.36			.08	.50
1000	82	4 (5%)	3 (4%)	5 (6%)	32	2 (6%)	1 (3%)	2 (6%)														
1048	25	1 (4%)	0	1 (4%)	7	0	0	0														
1065	20	1 (5%)	2 (10%)	2 (10%)	23	0	0	1 (4%)														
Protocol Total	106	6 (5%)	5 (5%)	8 (8%)	62	2 (3%)	1 (2%)	3 (5%)									.70	1.00				
1029	61	1 (2%)	3 (5%)	0					20	0	3 (15%)	1 (5%)										
1032	25	0	0	0					10	0	0	0										
1061	53	0	9 (9%)	7 (7%)					32	1 (3%)	3 (9%)	1 (3%)										
Protocol Total	105	1 (<1%)	12 (6%)	7 (4%)					62	1 (2%)	6 (10%)	2 (3%)							.36	.44		
Total Treatment Incidence	521	10 (2%)	29 (6%)	21 (4%)	218	3 (1%)	11 (5%)	6 (3%)	62	1 (2%)	6 (10%)	2 (3%)	153	6 (4%)	12 (8%)	1 (<1%)	1.00	.76	.62	1.00	<.01	.22

[ ] = Shaded areas not applicable to protocol design.

n = Number of patients with baseline and endpoint Part 1 EKGs.

EKGs were not required in this study.

* Abnormalities: N-A = Normal at baseline/abnormal at end of Part 1.
A-A = Abnormal at baseline/abnormal at end of Part 1.
A-N = Abnormal at baseline/normal at end of Part 1.

** Letter following statistically significant p-value indicates which treatment was favored in the analysis.

PHARM REVIEW

2-7-85

Review and Evaluation of the Pharmacology and Toxicology
and Clinical Data of
NDA 18-731

I have been asked to provide my comments for the labeling of BUSPAR as well as my portion of the SBA.

1. Labeling:

   a. Clinical Pharmacology

      (1) Although BUSPAR produces little or no sedation at 5-10 mg, there is some sedation at supratherapeutic doses.

      (2) Sentence 3 - In controlled clinical trial, subjects

   b. Use with alcohol:

      This section is acceptable as written.

   c. Drug Abuse and Dependence

      I suggest rewriting the section as follows:

      BUSPAR has been tested for abuse potential and dependence liability in both preclinical and clinical studies. In the preclinical studies, buspirone was not a positive reinforcing agent in a self-administration model in the rhesus monkey. In two clinical studies which utilized recreational drug abusers, buspirone was indistinguishable from placebo at 10 mg doses and produced dysphoric sedation at 40 mg single doses. Subject "liking" scores do not increase linearly with increasing drug dosage, suggesting a low ceiling for an abuse potential.

      In preclinical models, BUSPAR did not produce physical dependence of the sedative-hypotic type.

      The psychological dependence capacity of BUSPAR in patients is not known at this time, but available data suggest a low capacity psychological dependence of the type observed with sedative-hypnotic drugs.

2. BUSPAR SBA

Abuse potential and functional impairment capacity

Buspirone was tested for abuse potential in both preclinical and clinical paradigms. The preclinical test battery assessed drug self-administration, discriminative stimulus properties, physical dependence capacity and

interactive effects of buspirone with alcohol. The clinical studies assessed subjective effects in recreational drug abusers (2 studies) and the ability of buspirone to impair judgment and psychomotor performance, so-called functional impairment studies (6 studies). These studies will be summarized in the sections below.

Preclinical studies:

Buspirone was tested for primary physical dependence of the sedative-hypnotic type in the rat by subchronic (22 day) administration of up to 200 mg/kg/day. A comparison group was administered the same dosage of diazepam. Upon abrupt withdrawal, the diazepam-treated rats lost weight. The buspirone-treated animals gained weight during the post-administration period. Thus, there is no evidence that buspirone causes physical dependence in this model.

Buspirone was also tested in a substitution test in phenobarbital-dependent mice. An ability to substitute for a barbiturate in this model is consistent with sedative-hypnotic activity of the barbiturate type. In general, benzodiazepines partially-to-completely substitute for a barbiturate in this test. Buspirone, at doses of 50 mg/kg, failed to substitute in this test.

Psychopharmacologic testing of buspirone consisted of discriminative stimulus testing in rats and self-administration studies in rhesus monkeys. In the rat, buspirone's discriminative stimulus paroperties were compared to those of oxazepam and pentobarbital. Rats trained to discriminate buspirone from saline failed to recognize oxazepam or pentobarbital as buspirone-like. Other rats trained to discriminate pentobarbital from saline generalized to oxazepam but not buspirone. A third group of rats trained to discriminate oxazepam from saline generalized to pentobarbital but not buspirone. In an additional experiment, rats treated with either buspirone or oxazepam decreased operant responding for food. No cross tolerance was evident in this test, further suggesting dissimilar mechanisms of producing similar results.

Buspirone was tested for positive reinforcement capacity in cocaine-treated rhesus monkeys. (These animals were trained to press a lever for intravenous administration of 100 mg/kg of cocaine hydrochloride. Once behavior was stable (< 10% variation in injection rates across 3 sessions), test agents were substituted.) Buspirone was tested at 4 dose levels in 4 monkeys whereas chlorazepate and chlordiazepoxide was each tested in 2 animals. Buspirone maintained self-administraton in 1/4 monkeys; thus, under the conditions of the experiment, buspirone was considered non-reinforcing. Chlorazepate and chlordiazepoxide were also considered to lack positive reinforcement properties.

Drug interaction studies of buspirone in combination with CNS depressants were conducted in the mouse and the rat. Buspirone did not increase the hypnotic potency of hexobarbital or ethanol in either species.

A second experiment compared the effect of subhypnotic doses of hexobarbital or ethanol on the acute lethality curves generated with buspirone or

diazepam. Neithr hexobarbital nor ethanol potentiated the acute lethality of buspirone hexobarbital, and to a lesser extent ethanol, shifted the lethality curve of diazepam to the left.

Clinical studies:

The sponsor reported the effects of buspirone in two psychopharmacology studies to support a lack of abuse liability and 6 "functional impairment" studies to support a lack of effect on psychomotor performance. The interactive effects of buspirone and alcohol on subjective, objective and neurological impairment are found within the "functional impairment" studies. These studies will be summarized below.

The first abuse potential study was performed by Dr. [redacted] in recreational drug users. The study was a double-blind, randomized crossover in which each subject received oral doses of buspirone (10, 20 and 40 mg), diazepam (10 and 20 mg) and placebo. The primary subjective measurement items were the Addiction Research Center Inventory and the Single Dose Drug Questionnaire. Each administration was performed with a minimum 3-day washout interval.

Subjects discriminated between 10 and 20 mgs of diazepam and placebo as measured on the Single Dose Questionnaire and ARCI subscales. The subjective responses to buspirone were less consistent. Some sedation was indicated but only at the 40 mg level. The euphoria subscale discriminated 20 mgs buspirone from placebo, but not 10 or 40 mg conditions. The sponsor concluded that buspirone is unique in that subjective responses seen with acute therapeutic doses are not necessarily observed with larger doses. There is a suggestion that the effects of buspirone are inconsistent and not dose-related.

A second study conducted by Drs. [redacted] and [redacted] compared the abuse potential of buspirone, diazepam, methaqualone and placebo. The study design was double-blind, randomized, crossover in which subjects received 6 test preparations: 10 and 40 mgs of buspirone, 10 and 20 mgs diazepam, 300 mgs methaqualone, and placebo. Test materials were administered at 1-week intervals.

The primary dependent measure used was list 116 of the Addiction Research Center Inventory. Subjects were also asked to guess what drug they thought they had received, what rate they would pay for what they had received, and how high they felt during the session.

The recreational drug users failed to differentiate 10 mgs buspirone from placebo. Likewise, they could not differentiate between the 2 doses of diazepam, whereas the 2 doses of buspirone were significantly differentiable on 5 of 7 scales used. The high dose of buspirone and diazepam were not significantly different under the sedation scales. However, buspirone was clearly dysphoric at 40 mgs. Diazepam and methaqualone were the only drug treatments that produced significantly greater scores under one or both of the two euphoria subscales.

Buspirone caused lower mean scores on the abuse potential scale, whereas both methaqualone and diazepam produced significantly greater scores than the high dose of buspirone. Estimates of the street value and subject liking of the six treatment showed higher scores for methaqualone and 20 mgs diazepam that significantly differed from each other and from all the other treatments. Diazepam at 10 mgs fell in between. At the 1 hour time point, 69% and 53% of the subjects correctly identified methaqualone and 40 mgs of buspirone, respectively.

Dr. [redacted] concluded that in his study no abuse potential of buspirone was evident. This was due to the fact that the low dose of buspirone could not be differentiated from placebo, and the high dose of buspirone was clearly dysphoric, producing physical sedation and discomfort in the subjects.

Several studies were performed to assess the effects of buspirone on functional impairment capacity, i.e., driving skills related performance, information processing skills and psychomotor testing. In a study reported by [redacted] and [redacted]) acute and 8-day dosing of either 20 mgs of buspirone, 15 mgs of diazepam or placebo were administered to 24 men and 24 women. On days 1, 8 and 9 subjects were tested on a driving simulator and given 4 sessions of divided attention tasks examining tracking and visual search performance. On day 9, the subjects also received alcohol (men, 0.85 gms/kg; women, 0.72 gms/kg).

Twenty key performance measures in 5 categories from the simulator run were analyzed. These 5 categories were: tracking control, speed control, headway control, target detection, and emergency decision making. For each divided attention run, 4 variables were analyzed: response time, tracking control, combined errors, and a Z score (means of scores for response time and tracking, converted into Z scores). On the day that alcohol was administered, blood alcohol concentrations were measured 1 and 2 hours after the first alcohol dose. The mean blood alcohol concentrations for placebo, buspirone and diazepam were not significantly different across groups at either time point. In the acute dosing situation, the effects of diazepam and buspirone on performance were in opposite directions. The diazepam-treated group had the worst performance on the simulator measures, while the buspirone group did slightly better. The effects were significant at the 1-hour post-dose time only. However, the data suggest impairment due to diazepam up to 5 hours. The poorest performance of all three drug groups on tracking control, speed control, target protection and emergency decision-making was found in the diazepam group. Divided attention performance was also poorest in this group.

Subjects were tested on the same battery on day 8 in the pre-dose and post-dose situations. The pre-dose differences between the two drug groups and the placebo group were not marked. There was some evidence for poor performance in the diazepam group compared with both placebo and buspirone groups. However, differences between these two groups and the diazepam group before the 8-day treatment were much less than those seen after an acute dose of diazepam on the first test day. Following dosing in the respective groups,

performance differences among the three groups on the 8th day of treatment were similar in direction, but a greater magnitude of effects was observed than following a single dose. Performance decrement for diazepam worsened, whereas a slight improvement in performance was found with buspirone on day 8. Finally, impairment in the diazepam group relative to the buspirone group was greater on the 8th day.

On the 9th day of treatment, subjects were given alcohol along with their drug. The differences between the drug groups were much the same as those following treatment on the 8th day. However, the buspirone vs. diazepam differences were even more pronounced in favor of the buspirone group, with placebo differences less pronounced. As seen on the 8th day, the diazepam group performed worse than the placebo group, whereas the buspirone group performed better than the placebo group. Significant impairment for the diazepam group, compared to both placebo and buspirone groups, lasted up to 5 hours after treatment when alcohol was added. The results suggest an impairment produced by diazepam on skills performance after both acute and 8-day dosing. This impairment is worsened in combination with alcohol. In contrast, buspirone produces either no effect or a slight increase in performance in an acute or 8-day dosing. When combined with alcohol, buspirone appears to actually offset some of the impairment due to alcohol administration. It is not known whether this offsetting effect is of a sufficient magnitude to be clinically meaningful.

A second study (Study #1003) compared the effects of buspirone, diazepam and placebo with, or without, alcohol in a test battery which included driving simulation and other non-simulation tests. The driving simulation test allowed testing of performance on a set of tests similar to on-the-road driving. The non-simulator tests were measures of cognitive function (the visual backward masking tests and the word frequency test), a measure of balance in gross body control (the body sway test), and a measure of hand-eye coordination (the hand steadiness test).

The study design was a double-blind, randomized Latin Square design using a 2 x 3 factorial with drugs as a within-group variable and alcohol as a between-group variable; i.e., one group of subjects received the three treatments without alcohol in three successive sessions and a second group received them in combination with alcohol. The three drug doses were 10 mg buspirone, 10 mg diazepam, and placebo. Subjects were also asked to rate the following subjective parameters: estimates of overall performance on a scale of 1-5; estimate whether the dosage form received was active drug or placebo; indicate whether the beverage received was alcoholic or non-alcoholic.

Subjects completed six training runs in the driving simulator and non-simulator tests. An analysis of covariance was used to account for group trends or differences noted in the training runs. There was no covariate analysis used for the non-simulator tests. If an overall test comparison of the three drug treatments was less than p = .1, pairwise treatment comparisons for alcohol and non-alcohol groups were performed using a p value .05 to assign statistical significance.

In terms of alcohol-related effects, multiple performance decrements were noted in a driving simulation test. When diazepam alone was compared to placebo, 11 performance measures showed a significant decrement following diazepam administration in this simulator task. When buspirone was compared to placebo, there was essentially no difference in the performance. In effect, 10 mg of buspirone was shown to be non-impairing. When buspirone was compared to diazepam, buspirone produced less performance decrement on 7 variables and a trend towards less decrement in 5 other variables. Overall the results suggest that buspirone causes no more functional impairment than placebo, whereas diazepam (10 mgs) produces significant impairment in driving performance.

Diazepam, when compared to placebo treatment, showed significant impairment on all three measures of the visual backward masking test. Buspirone was better than placebo at the intermediate interstimulus interval and significantly better than diazepam at both the fast and intermediate interstimulus intervals. The results in this test showed different effects for diazepam and buspirone. Diazepam produced a decrement in the visual backward masking test, whereas buspirone actually produced a slight improvement relative to placebo. In the measures of gross motor performance (the hand steadiness test and the body sway test), diazepam produced significantly poorer performance when compared to both buspirone and placebo. Buspirone was not significantly different from placebo in the hand steadiness test, although buspirone caused an increase in the number of lateral excursions when compared to diazepam and placebo in the body sway test.

When the subjective estimates of performance were analyzed, subjects in the alcohol group indicated a slightly poorer performance under placebo than either of the active drugs. Subjects in the no-alcohol group indicated their best performance occurred under placebo followed by diazepam, and their worst performance under buspirone. The latter subjective estimate is interesting when compared to the results of the objective measures under the simulator and non-simulator tests. Diazepam subjects felt they performed well, but in reality their function was impaired. In contrast, buspirone was not really impairing, but subjects felt their performance was impaired. The results suggest that both drugs produce perceptual, judgmental, amnestic or affective disturbances which tend to underestimate the performance decrement in the case of diazepam, and overestimate any performance decrement in the case of buspirone. The results also indicated that buspirone does not possess additive depressant effects in the presence of alcohol.

Another study comparing buspirone, diazepam and placebo with, or without, alcohol was performed by [redacted] (Study No. 1290) at the [redacted]. The purpose of the study was to compare the effects of buspirone, diazepam and placebo administered alone, or in combination with alcohol on certain psychomotor and information processing activities in healthy adult male subjects. Twenty-four (24) male subjects were randomly assigned to groups of 12 subjects each; the alcohol group was to receive an alcoholic beverage expected to produce a peak blood alcohol level of 0.08%. The drug treatments were 10 and 20 mgs of buspirone, 10 mgs

diazepam, and placebo. A two-week period intervened between each of the four treatment/testing sessions. The study design was a double-blind, randomized type using a 2 x 4 factorial with drugs as a within group variable, and alcohol as a between group variable. At each treatment session, the test battery was administered before and after drug/beverage ingestion. The post-drug testing was performed at 1 and 3 hours after administration of drug. The test battery included various measures of balance and body control, tracking skills, and information processing capacities. The specific tests used were the standing steadiness test, a continuous subcritical tracking test, an adaptive tracking test, a continuous performance test, a divided attention test, a spatial information processing test, a visual vigilance test, a reaction time test, and visual and auditory evoked responses.

Baseline performance scores were analyzed for the alcohol vs. "no alcohol" group. There were no strong differences present in any of the variables. All data were pooled for subsequent analyses.

When the alcohol and "no alcohol" treatments were compared, there was a significant difference in three variables and a trend towards significance in three more variables. Alcohol was associated generally with poor control in all performance variables. Alcohol was associated with significant, or near significant, impairments in tracking skills as per the results of the continuous subcritical tracking and adaptor tracking tests. The visual vigilance test showed poor responses under alcohol. Reaction time under the visual vigilance test was significantly impaired in the alcohol group. At the one-hour timepoint, a significant ($P < 0.001$) drug by beverage interaction occurred in reaction time measured in the visual vigilance test. This is due primarily to the contrasting reaction times between diazepam and placebo. There was some decrement in the buspirone groups but the effect was not as marked as that with diazepam. The effect of diazepam was one of marked impairment. In the visual vigilance test, the rank order of impairment was placebo<10 mg buspirone < 20 mg buspirone < 10 mg diazepam. The buspirone differences were significantly different from placebo but not from each other. The buspirone (10 and 20 mg) differences from diazepam were significantly different.

No differentiation in performance was noted in four of the tests at one hour after administration of the four test drugs. These included the two tracking tests (continual subcritical tracking and adaptive tracking), the continuous performance test and the simple reaction time test. On the other hand, the standing steadiness test differentiated diazepam from both doses of buspirone and placebo. Here both buspirone doses were not different from placebo (except where 10 mgs of buspirone showed significant improvement in one of the four variables). Diazepam showed impairment when compared to the other three drugs and particularly so when compared to 10 mgs buspirone.

Diazepam showed impairments of performance relative to buspirone and placebo in the divided attention test. Both buspirone doses were indistinguishable from placebo.

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Diazepam showed impairments of performance relative to buspirone and placebo in the divided attention test. Both buspirone doses were indistinguishable from placebo.

Buspirone (20 mg) and diazepam, without differing significantly from each other, significantly impaired performance relative to placebo in the spatial information processing test. At 3 hours post-drug administration, diazepam-placebo differences were observed on 9 of the 12 measures of performance. Buspirone (10 and 20 mgs) was indistinguishable from placebo. When diazepam-buspirone (10 mg) comparisons were made, the effects of buspirone were superior to diazepam in 6 of 12 tests and marginally superior in another period. When 20 mgs of buspirone was compared to diazepam, the effects of buspirone were superior in 7 measures of performance. The results of this study demonstrate that the two doses of buspirone with, or without, alcohol affect the performance profile in a manner similar to placebo with, or without, alcohol. In contrast, diazepam with, or without, alcohol affects the performance profile in a manner different from that of placebo. The effect of diazepam is clearly in the direction of increased functional impairment.

A fourth study (Study #427) compared the effects 10 and 20 mgs of buspirone, lorazepam 2.5 mgs, and placebo, with and without alcohol, on psychomotor skills and subjective states in healthy male subjects. The experimental design was a double-blind, controlled crossover study in which each subject received 8 different treatments (drug and drink combinations) at weekly intervals in a randomized order.

The subjects were trained on a battery of tests. On each study day they were again administered the testing before, and 90 and 180 minutes after treatment.

The following battery of tests was selected to measure psychomotor performance and information processing ability: body sway (recorded with subject's eyes open and closed); hand steadiness; compression forced test (hand grip); tapping rate; flicker fusion test; tracking test (coordination test); choice reaction test; maddox wing test (measurement of extraocular muscle balance); horizontal nystagmus; and blood alcohol concentration. Additionally, subjective assessments were made of ability to perform, degree of intoxication, and some of the psychological effects of treatments recorded on a visual analog scale. Subjects were also asked to rate the drugs as tranquilizing, stimulating or placebo and the drinks as alcoholic or non-alcoholic.

A 42-item questionnaire was employed to assess the side effects of treatment.

In the body sway test, there was no significant drug by alcohol interaction for lateral sway. The drug effects were significant. Lorazepam significantly increased body sway as compared with the upper dose of buspirone or placebo. With eyes closed, the lorazepam-induced sway was most marked and was significantly worse than other treatments (with, and without, alcohol). Buspirone (10 or 20 mgs) did not affect body balance.

For saggital sway, there was a significant drug by alcohol interaction. There was also a significant drug effect on sagittal sway. While body balance was significantly affected by all alcohol drug treatments, there were no

significant differences among treatments in the alcohol-free groups. In the alcohol-treated groups, lorazepam caused significantly greater sway than placebo and both doses of buspirone.

The drug effect on total body sway was significant. There was also a significant drug by alcohol interaction. The interaction of lorazepam and alcohol appears to have potentiated the effect of both drugs. The effects of buspirone 20 mg plus alcohol appeared to be purely additive.

On the hand-steadiness test, the drug effect and drug by alcohol interaction effect were significant. This was due to a significant improvement after buspirone 10 mgs plus alcohol compared to all other alcohol treated groups. No differences were seen among the alcohol-free treatments.

Critical flicker fusion recognition was significantly impaired with lorazepam as compared to either dose of buspirone or placebo. The 20 mg dose of buspirone significantly impaired critical flicker frequency as compared with placebo. In the tracking test, there was no significant drug by alcohol interaction. Drug effects were significant. The subjects made more mistakes after lorazepam than after buspirone 10 mgs or placebo. Buspirone in the upper dose also caused significantly more mistakes than placebo. When the data were calculated as a percentage of mistakes, lorazepam had a significantly higher error rate than placebo and both doses of buspirone.

In the choice reaction test, there was a significant drug effect recorded. The number of incorrect responses was higher after lorazepam as compared with 10 mgs of buspirone. In terms of cumulative time, lorazepam significantly impaired timing compared to both doses of buspirone or placebo.

In the Maddox Wing test, there was a significant drug effect, but no drug by alcohol interactions. Subjects were significantly more impaired after lorazepam than after the lower dose of buspirone or placebo.

In the nystagmus test, there was a significant drug by alcohol interaction as well as a significant drug effect for left nystagmus. This was primarily due to a marked degree of impairment caused by alcohol. Significant nystagmus was seen in all subjects on alcohol plus drugs. Among the alcohol-free treatments only the lorazepam caused more nystagmus than placebo, while in the alcohol treated groups, 10 mg buspirone actually showed significantly less nystagmus than the other treatments.

On subjective tests, there were significant drug and drug by alcohol effects. As compared with lorazepam alone, subjects reported significant improvement in alertness with lorazepam plus alcohol. The higher dose of buspirone plus alcohol significantly decreased alertness as compared with buspirone 20 mgs alone.

All active treatments (without alcohol) caused subjects to feel markedly less contented than did placebo. However, with lorazepam plus alcohol, subjects reported being significantly more contented than during treatment with lorazepam alone.

On two of the visual analog scales (contented/discontented and attentive/dreamy subjective tests) there was significant drug effects and drug by alcohol interactions. Subjects felt more contented on alcohol alone, or on alcohol plus the low dose of buspirone, or on alcohol plus lorazepam. Lorazepam subjects felt less contented or attentive than placebo while opposite changes were recorded when lorazepam plus alcohol was ingested. On the majority of the mood scales, 20 mgs of buspirone gave negative responses compared to placebo. The subjects felt more "feeble, sad, antagonistic, bored, depressed, self-centered and mentally slow." Lorazepam was only worse than placebo on two mood scales (bored and depressed).

Interestingly, when subjects were asked to rate their performance, they claimed that 20 mgs of buspirone caused significant decrement relative to placebo. When subjects were asked to rate drunkenness, there was no significant drug by alcohol interaction. However, the drug effect was significant. Subjects felt slightly more intoxicated after 20 mgs of buspirone than after 10 mgs or placebo.

Subjects correctly identified the drinks as alcoholic or non-alcoholic. They were, however, less accurate in identifying the drugs as tranquilizers, stimulants or placebos. The upper dose of buspirone was almost always correctly identified as a tranquilizer, while lorazepam plus alcohol confused the subjects. They identified this combination as a placebo in 17 of 23 responses.

The objective performances and the subjective appraisal of those performances are discordant. There is an objective psychomotor decrement caused by a single oral dose of lorazepam. This decrement is even more pronounced in the presence of alcohol. However, subjects do not perceive that any performance difficulties are encountered. Paradoxically, buspirone 10 and 20 mgs causes little, if any, performance decrement but the negative mood changes that occur apparently cause a misperception of psychomotor performance decrement. Buspirone, in combination with alcohol, produces effects which are essentially those seen with alcohol alone.

The psychopharmacologic effects of acute single doses of buspirone, diazepam and placebo were studied by Drs. [redacted] and [redacted] (Study #326). The study design was a double-blind, crossover study. The order of drug administration was designated according to a balanced Latin Square design. Subjects were tested prior to each treatment and at 1, 3, and 5 hours after the dose. The doses used were a 10 mg dose of diazepam compared to 10 and 20 mgs of buspirone and placebo. The inter-administration interval between treatments was a minimum of one week.

The following psychometric tests were performed: digit symbol substitution test; the symbol copying test; tapping rate; and auditory reaction time. Mood scales which measured 16 parameters of mood on visual analog scales were administered. A bodily symptom scale was also used. Fourteen side effects were listed and the subjects rated them between absent and severe. Additionally, an electroencephalogram was recorded. A wave band analysis was performed on the EEG.

In the digit symbol substitution test, diazepam significantly decreased the number of items completed correctly in comparison to both doses of buspirone and placebo. In the symbol copying test, diazepam caused significantly more impairment as compared with placebo or the lower dose of buspirone. There was significantly more impairment following the higher dose of buspirone as compared with the lower dose of buspirone. Diazepam produced a longer inter-tapping interval. However, this was not statistically significant.

Analysis of the auditory reaction time data noted that both the diazepam and the high dose buspirone produced significant decreases in the speed of reaction time in comparison to placebo. The high dose of buspirone also produced a significant decrement in reaction time as compared with the low dose of buspirone.

Buspirone and diazepam had dissimilar effects on the electroencephalogram.

Analysis of the mood rating scale data noted that there was a significant drug effect accompanied by a significant drug by hour interaction for alertness. At one hour, both doses of buspirone and diazepam produced more sedation than placebo. However, at 5 hours there was an improvement in alertness in the diazepam group. There were significant differences among the four treatments in terms of the calmness factor. Subjects felt significantly less calm after the higher dose of buspirone than after the other treatments. When the bodily symptoms scale was analyzed, significantly more severe side effects were observed with the 20 mg dose of buspirone. The lower dose of buspirone produced more side effects than placebo on only three symptoms (anxiety, sweating and shaking). Diazepam increased anxiety and dizziness compared to placebo. Dizziness after diazepam was significantly greater than after the 10 mg dose of buspirone.

The results suggest that buspirone produces far less impairment on the psychometric tests than 10 mgs of diazepam. Moreover, the higher dose of buspirone (20 mgs) appears to have dysphoric side effects which may limit the clinical dose escalation, as well as the abuse potential of the substance.

A companion study to the single dose study was performed by Drs. [redacted] and [redacted] (Study #470). This was a double-blind crossover study in which subjects received four drug treatments with a minimum of a one-week washout period between treatments. Subjects received either 5 mgs of diazepam three times a day, or 5 or 10 mgs of buspirone three times a day, or placebo for one week.

Subjects were tested before each treatment and at 1 and 3 hours after the first dose on day 1. They were also tested before the first daily dose and at 1 and 3 hours after dosing on days 3 and 8. Psychological, subjective, and physiological test measures were administered. The psychological measures included the digit symbol substitution test, the symbol copying test, tapping rate and the auditory reaction time. The subjective effects were a mood rating scale (visual analog) and a bodily symptom scale with 14 side effects listed. Physiological measures included the broad wave band analysis of the electroencephalogram, a power analysis of the band widths and an auditory evoked response.

Diazepam produced significant impairment on the digit symbol substitution test. When the symbol copying test was analyzed, sequence and interaction effects were not significant. However, diazepam caused significantly more impairment compared to placebo or buspirone (5 mgs t.i.d.).

When the mood scores were analyzed, there was a significant difference in the amount of contentedness between the 5 mg buspirone dose regimen and the placebo and diazepam dose regimens. Other changes noted were that the 5 and 10 mg dose regimens of buspirone made subjects feel dreamier than placebo or diazepam treatments. Additionally, the 10 mg t.i.d. regimen made subjects feel less proficient than the other treatments.

Analysis of the bodily symptom scale data revealed there was a significant treatment effect accompanied by significant drug by time interaction for dizziness. This was primarily due to an improving trend over time for buspirone relative to diazepam or placebo.

Significant differences were observed among the four treatment groups for sweating, shaking, palpitations, restlessness, muscular tension, physical tiredness, dizziness and indigestion.

Only dizziness was seen with each treatment. It was more persistent with the higher doses of buspirone and diazepam. Physical tiredness and indigestion were significantly lower with buspirone, 10 mgs, as compared with either diazepam or placebo. The physical tiredness was also significantly lower with buspirone as compared with diazepam. Additionally, several subjects volunteered side effects. Three subjects reported some dizziness on standing or walking while on the high dose of buspirone. However, this effect wore off by day 8. One subject reported dizziness following the lower dose of buspirone. Diazepam was associated with drowsiness reported by 4 of 8 subjects. Two subjects on diazepam also reported they enjoyed the treatment.

Buspirone had very little effect on the electroencephalogram, whereas diazepam showed increased activity and the alpha and beta wave length wave band groups.

Overall, the effects of a one-week dose of buspirone are no greater than those observed after a single dose administration. In fact, due to the differences in dosage administration, 5 and 10 mgs t.i.d., vs. 10 and 20 in a single dose, certain effects were not obtained in the second study, notably dysphoria at the 20 mg dose. Although a higher daily dose (30 mgs) was administered in the 7-day study, the 10 mg dose may be below the threshold for development of dysphoric effects. Dizziness tended to wear off in the buspirone-treated groups as the week went on.

Summary:

Buspirone did not produce physical dependence as assessed in the rodent models. Neither buspirone nor the two benzodiazepines demonstrated positive reinforcement properties in the rhesus monkey.

Buspirone's effects in two psychopharmacological studies suggest a lack of abuse potential because of its subtle effects at clinical doses and dysphoric responses at high doses. Data from these two studies formed the basis for the decision not to schedule buspirone under the Controlled Substances Act. The Drug Abuse Advisory Committee agreed that buspirone is lacking in sufficient abuse potential to warrant scheduling (see attached minutes of meeting, Section).

Buspirone does not appear to have additive depressant effects in conjunction with hexobarbital and alcohol in animal models or in conjunction with alcohol in clinical tests.

Buspirone appears to produce few significant cognitive and psychomotor deficits. It appears to produce a perceptual defect with respect to judgment of actual performance; i.e., subjects report that performance is impaired when it is not.

Buspirone appears to cause dizziness and sedation at doses of greater than 10 mg. There is some evidence of tolerance development to the dizziness.

Frank J. Vocci Jr.

Frank J. Vocci, Jr., Ph.D.

cc:
NDA Orig
HFN-220
HFN-120
HFN-120/FVocci/12/28/84
Edit:FVocci/2/1/85
FT:dcm/1/25;2/1/85
DOC #0153d

PHARMACOLOGY REVIEW OF NDA 18-731
Amendment of July 5, 1984.

Sponsor: Bristol Myers
Evansville, Indiana

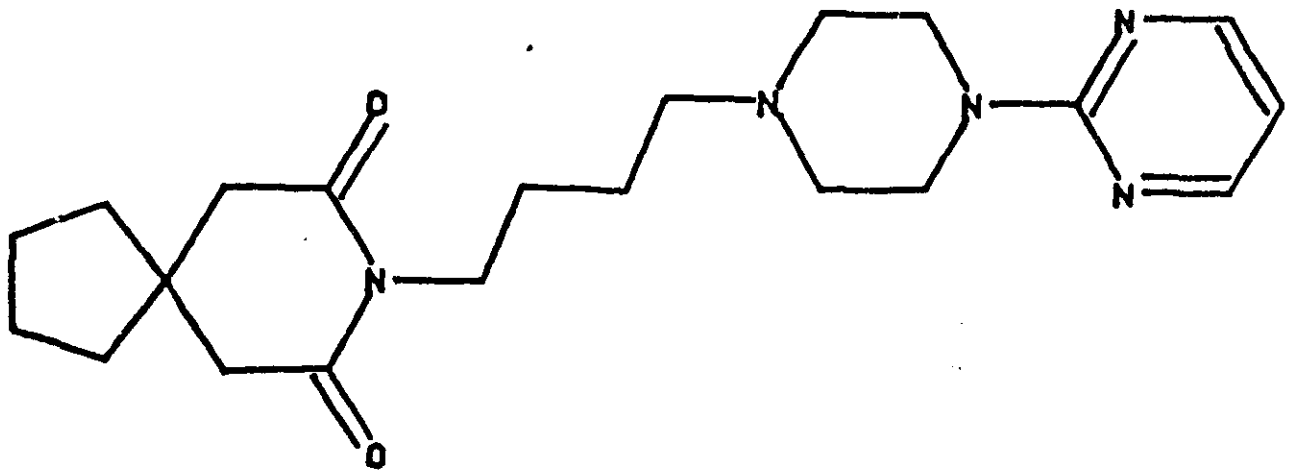
19

Drug: Buspar (buspirone)

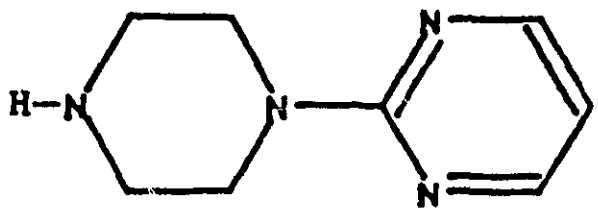
Background:

At a meeting between FDA and Bristol Myers of March 28, 1984, there was a discussion of the metabolism of buspirine to 1-PP, the major active metabolite. Specifically we wanted to know how much 1-PP was present in plasma after doses of buspirone comparable to those used in rat toxicity studies (i.e. up to 200 mg/kg). We also wanted to know what the plasma levels of 1-PP were in man after therapeutic doses of buspirone. The following submission is in response to those questions.

Structures of the compounds in question:



MJ 9022 (Buspirone)



MJK 13653 (1-PP)

The plasma level values of buspirone for these subjects are shown in the Sponsor's table:

PLASMA CONCENTRATION OF BUSPIRONE IN NON-SMOKING SUBJECTS IN CLINICAL STUDY 1669

Subject	Day / Time (hr)	1 / 0	1 / 24	2 / 24	3 / 24	4 / 24	5 / 0.5	5 / 1	5 / 1.5
2		*	*	0.36	0.24	0.42	2.42	2.86	2.23
3		*	0.08	0.33	0.40	0.38	2.00	1.62	1.06
4		*	0.07	0.18	0.17	0.17	0.80	1.03	0.55
6		*	0.13	0.60	0.48	0.54	2.63	2.63	1.45
7		*	*	0.14	0.20	0.18	0.50	0.55	0.09
9		*	*	0.20	0.27	0.25	0.97	1.13	0.88
10		*	*	0.14	0.14	0.17	1.14	1.11	1.11
11		*	0.05	0.23	0.11	0.18	0.48	0.56	0.39
12		*	0.05	0.28	0.57	0.33	2.71	2.96	2.30
13		*	0.09	0.30	0.28	*	1.67	1.12	0.98
14		*	*	0.15	0.13	0.16	0.80	0.56	0.58
19		*	0.09	0.37	0.37	0.31	1.99	1.99	1.86
21		*	*	0.17	0.26	0.21	1.64	1.59	1.52
22		*	0.06	0.34	0.52	0.43	1.57	1.57	1.34
23		*	0.06	0.27	0.25	0.38	4.86	4.51	2.70
25		*	0.14	0.60	0.71	1.00	2.13	3.16	2.18
26		*	*	0.17	0.09	0.09	0.31	0.72	0.52
28		*	0.06	0.23	0.40	0.29	1.15	1.05	0.97
29		*	0.10	0.36	0.44	0.56	4.00	3.93	2.11
31		*	*	0.12	0.34	0.26	3.23	2.26	1.36
35		*	0.25	0.94	1.06	1.14	6.00	6.60	4.50
37		*	0.13	0.36	0.40	0.40	2.27	1.83	1.30
39		*	0.11	0.46	0.67	1.14	11.05	5.41	5.17
41		*	*	0.24	0.36	0.24	0.41	0.74	0.74
43		*	*	0.12	0.17	0.21	0.22	0.43	0.89
44		*	0.08	0.32	0.36	0.65	3.76	5.63	2.34
48		*	*	0.14	0.16	0.19	1.17	1.07	0.86

* Less than 0.04 ng/ml

Studies Submitted and Summary of Results:

1. MAYO-RF-10376

Methods:

Forty-eight subjects (12 women and 12 men, 18-40 yr; 12 women and 12 men, greater than 65 yr). Each subject received a 15 mg oral dose of buspirone on Day 1 followed by 15 mg q 8 hr on Days 2-4 and a single 15 mg dose on Day 5 at 8 hr following the previous dose. The 8 samples/subject analyzed were taken prior to drug treatment, prior to the morning dose on Days 2-5 and at 0.5, 1 and 2 hr following the dose on Day 5. Thus, a drug free control sample, 4 estimates of C_{min} and 3 samples which would be expected to contain the highest concentrations of buspirone and 1-PP were evaluated for each subject.

During evaluation of plasma standards prior to analysis, it became evident that plasma samples from some individuals contained significant quantities of a substance which interfered with the determination of 1-PP. It was found that plasma from individuals who used tobacco products contained this interfering substance. The presence of this peak precluded quantification of the 1-PP concentration in samples from these subjects.

Results:

The extent of the interference present in the plasma of 13 of these subjects was less than 30 ng 1-PP equivalents/ml and no apparent inceases in the peak could be detected after dosing, and suggesting that there was not a marked accumulation of 1-PP. Samples from the remaining smokers had values in the 100-500 ng/ml range. The other 27 non-smoker subjects, which contained no interfering peaks, did not contain quantifiable levels of 1-PP. Two subjects showed highest levels of 22 and 24 ng/ml in individual samples, and 12 of the subjects showed a detectable peak between 10 and 20 ng/ml in their highest sample. Seven subjects showed no detectable 1-PP in any of the samples. The highest detectable value at 1 hr on Day 5 was approximately 14 ng/ml.

These data suggest that the plasma concentration of 1-PP did not exceed 25 ng/ml.

2. MAYO-RF-10422:

Methods:

Study 1480 was a 32-day study in which both female and male patients were administered Buspirone at doses of 10 mg single dose initially, increasing to 30 mg (10 mg t.i.d.) on Day 7. This dose of 30 mg/day was continued to Day 28. Blood samples were taken on Days 1, 14, 28 and 32 (placebo).

Samples were also obtained from ongoing Clinical Studies 1345, 1610 and 1630 from 6 patients who were non-smokers and who had been taking buspirone at 30-50 mg/day for periods of 3-4 weeks. Samples were obtained at between 1 and 5 hr post-dose.

Results:

Study 1480 - No quantifiable levels of 1-PP were found in any of the samples. All but 3 of the samples showed a detectable peak ranging between 10 and 16 ng/ml.
Studies 1345, 1610 and 1630 - No quantifiable levels of 1-PP were found in any of the 6 samples. Two samples showed detectable peaks of approximately 11 ng/ml.

Thus, concentrations of plasma 1-PP did not exceed 25 ng/ml after 28 days of dosing with 30 mg or 3 to 4 weeks of dosing with 30-50 mg buspirone.

3. MAYO-RF-10406:

Methods:

Male and female rats were given an aqueous solution of buspirone at daily doses of 0, 50, 100 and 200 mg/kg/day (divided in 2 equal doses) for 5 days by gavage. Groups of 3 male and 3 female rats from each of the drug-treated groups were blead at 0, 1, 3, and 6 hr following the last dose (Day 5).

Results:

Plasma levels of buspirone in the female rats were markedly higher than in males, especially in the HD group at 3 hr. Conversely, plasma levels of 1-PP show the opposite results, being higher in males than in females. This is consistent with reported higher levels of mixed-function oxidases in male versus female rats.

Plasma level values are shown in the following tables from the sponsor:

TABLE II

CONCENTRATION OF 1-PYRIMIDINYLPIPERAZINE (1-PP) IN PLASMA OF RATS AFTER ADMINISTRATION OF BUSPIRONE BY GAVAGE AT 50, 100 AND 200 MG/KG/DAY FOR FIVE DAYS[a]
MAP STUDY 854-MJ9022-03; 4/3/84

DOSE mg/kg/day	SEX: TIME AFTER DOSING (hrs):	1-PP (ng/ml Plasma) MALE 0	MALE 1	MALE 3	MALE 6	FEMALE 0	FEMALE 1	FEMALE 3	FEMALE 6
0		*	NS	NS	NS	*	NS	NS	NS
		*	NS	NS	NS	*	NS	NS	NS
		*	NS	NS	NS	*	NS	NS	NS
50		*	538	251	26	38	*	117	52
		*	410	270	77	*	91	86	80
		*	396	156	109	*	219	80	67
	Mean	*	448	226	71	13	103	94	66
	±S.D.		±78	±61	±42	±22	±110	±20	±14
100		*	840	707	315	*	204	169	311
		*	617	635	265	*	184	313	246
		*	602	476	343	*	239	325	138
	Mean	*	686	606	308	*	209	269	232
	±S.D.		±133	±118	±40		±28	±87	±87
200		99	918	906	759	353	709	899	458
		93	699	895	621	36	343	654	375
		244	606	904	305	*	555	875	455
	Mean	145	741	902	562	130	536	809	429
	±S.D.	±86	±160	±6	±233	±194	±184	±135	±47

[a] Animals were sacrificed at the designated times after the dose on the fifth day. Each data point represents a single animal.

* <25 ng/ml.

NS No Sample Taken.

TABLE III

CONCENTRATION OF BUSPIRONE (BU) IN PLASMA OF RATS AFTER ADMINISTRATION OF BUSPIRONE BY GAVAGE AT 50, 100 AND 200 MG/KG/DAY FOR FIVE DAYS[a]
MAP STUDY 854-MJ9022-03; 4/3/84

DOSE mg/kg/day	SEX:	BUSPIRONE (ng/ml Plasma) MALE				FEMALE			
	TIME AFTER DOSING (hrs):	0	1	3	6	0	1	3	6
0		*	NS	NS	NS	*	NS	NS	NS
		*	NS	NS	NS	*	NS	NS	NS
		*	NS	NS	NS	*	NS	NS	NS
50		*	514	10.5	115	QNS	0.6	36.3	30.8
		*	242	*	*	*	429	56.0	46.8
		*	38.3	*	*	1.2	4809	64.0	106
	Mean	*	265	3.5	38.3	0.6	1746	52.1	61.2
	±S.D.		±239	±6.1	±66.4	±0.7	±2661	±14.3	±39.6
100		QNS	843	130	*	*	429	737	124
		11.6	236	178	*	QNS	860	799	380
		*	24.0	68.2	7.0	62.4	325	182	244
	Mean	5.8	368	125	2.3	31.2	538	573	249
	±S.D.	8.2	±425	±55.0	±4.0	±44.1	±284	±340	±128
200		*	130	191	5.9	182	737	10011	90.1
		*	297	654	6.1	0.9	231	6075	65.4
		74.3	153	231	130	1.4	231	4809	180
	Mean	24.8	193	360	47.3	61.4	400	6965	112
	±S.D.	±42.9	±90.5	±258	±71.6	±104	±292	±2712	±60.3

[a] Animals were sacrificed at the designated times after the dose on the fifth day. Each data point represents a single animal

* <0.05 ng/ml
NS No Sample Taken
QNS Quantity Not Sufficient

AUC values from the mean plasma level data for 1-PP are higher than the values for buspirone in male rats at all dose levels and are lower than the values for buspirone in female rats at all dose levels. In both sexes, the AUC values for 1-PP show a linear relationship to the dose administered.

AUC values are shown in the following table from the sponsor:

MEAN PLASMA CONCENTRATION OF 1-PYRIMIDINYLPIPERAZINE (1-PP) AND BUSPIRONE (BU) IN RATS AFTER ADMINISTRATION OF BUSPIRONE BY GAVAGE AT 50, 100 AND 200 MG/KG/DAY FOR FIVE DAYS[a]

		MEAN CONCENTRATIONS (ng/ml Plasma)									
	SEX:	MALE					FEMALE				
	TIME AFTER DOSING (hrs):	0	1	3	6	AUC[b]	0	1	3	6	AUC[b]
DOSE (mg/kg/day)	COMPOUND MEASURED										
50	BU	*	265	3.5	38.3	464	0.4	964	52.1	61.2	2841
	1-PP	*	448	226	71	1343	13	103	94	66	495
100	BU	5.8	368	125	2.3	871	31.2	538	573	249	2629
	1-PP	*	686	606	308	3006	*	209	269	232	1334
200	BU	24.8	193	360	47.3	1273	61.4	400	4003	112	18211
	1-PP	145	741	902	562	4282	130	536	809	429	3535

a Animals were sacrificed at the designated times after the dose on the fifth day. Each data point represents the mean of 3 animals.
b ng·hr/ml

CONCLUSION:

Doses of 30-50 mg/day for 28 days results in plasma levels of 1-PP which are less than 25 ng/ml. In contrast, 1-PP levels in all rat plasma samples obtained at doses similar to those used in the oral toxicity studies were substantially higher (400 to 900 ng/ml).
The sponsor feels these data support the safety of buspirone in terms of its conversion to 1-PP after buspirone administration since there were no pronounced effects during toxicity tests in rats, and humans have much lower (non-quantifiable) levels of circulating 1-PP after therapeutic doses of buspirone for up to 28 days.

RECOMMENDATIONS:

I feel that the sponsor has addequately addressed this issue and that there is no cause for concern regarding plasma levels of 1-PP during buspirone treatment.

Jerry M. Cott

Jerry M. Cott, Ph.D.

cc:
Orig. NDA 18-731
HFN-120
HFN-340
HFN-120/JCott/7-10-84
HFN-120/Contrera rd/AJackson/7-10-84 DC 7/14/84
Doc. 1285C

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JC 7/14/84

ORIG NDA

SEP 21 1983

NDA 18-731

Reviewer: Jerry M. Cott, Ph.D.
Submission Date: 12/15/82

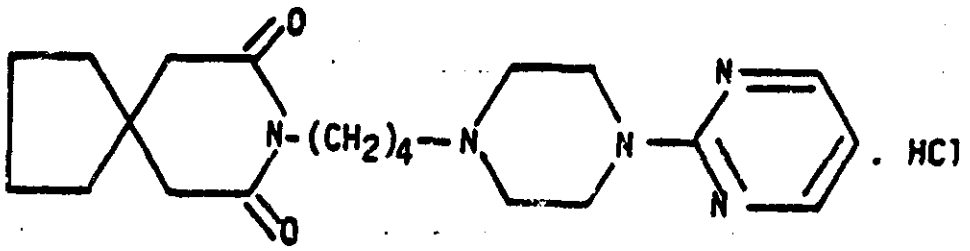
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

SPONSOR: Bristol-Myers Co.
Evansville, Indiana

DRUG:

1. Generic: Buspirone hydrochloride
2. Trade: Buspar™
3. Company No.: MJ 9022-1
4. Chemical Name and Structure:

8- 4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl -8-azaspiro [4.5] decane-7,9-dione hydrochloride



PHARMACOLOGIC CATEGORY: Antianxiety Agent

PROPOSED INDICATION: Therapy of anxiety disorders with and without accompanying depression.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: 5 and 10 mg scored tablets for oral administration.

RELATED DRUGS/INDs/NDAs: MJ 13859 (antipsychotic)
MJ 13805 (anxiolytic)

PRECLINICAL STUDIES REVIEWED:

I. PHARMACOLOGY-Vol. 1.14, 1.15, 1.16

A. CNS Effects.
   1. Anxiolytic activity
   2. Sedative activity
   3. Anticonvulsant
   4. Muscle relaxation
   5. Electrophysiologic activity
   6. Miscellaneous

B. Neurochemistry.

C. Cardiovascular, Respiratory and Renal System Effects. Lots 2, 3, and 4.

D. Smooth Muscle and Autonomic Activity

E. Endocrine Effects

F. Miscellaneous

II. PHARMACOKINETICS - Vol.

A. Absorption - rat, monkey
B. Distribution - rat, monkey
C. Metabolism - rat, monkey
D. Excretion - rat, monkey

III. TOXICOLOGY

A. Acute Toxicity- Rat, Mouse, Dog, Monkey (Lot 3, 5)

B. Range Finding Studies
   1. Rat - Lot 3
   2. Mouse - Lot 5
   3. Dog - Lot 5

C. Subchronic
   1. Rat - 90 day (Lot 5)
   2. Monkey - 90 day (Lot 5)

D. Chronic
   1. Rat (1 yr interim study of 2 yr study see Under E.1.) Lot 3MDE009.
   2. Monkey - 1 yr Study (Lots 3MDE009 and 3MDA049).Conducted at

E. Carcinogenicity
   1. Two yr rat- Lots 3MDE009, 3MJE054, and 3MEA094.
   2. Eighteen Month Mouse- Lot 12.

F. Special Studies
   1. Drug Interactions
   2. Allergenic Potential

IV. REPRODUCTION STUDIES:

A. Segment I - Rat. Lot 12.
   1. Treated Female
   2. Treated Male
   3. Both Treated

B. Segment II. Lot 5.
   1. Rat
   2. Rabbit

C. Segment III - Rat. Lot 5.

D. Mutagenicity
   1. Ames Test. Lot 3MDN162.
   2. Mouse Lymphoma Mutagenesis Assay. lot MA T1791, Microbiological Associates
   3. Unscheduled DNA Synthesis. Lot 32.
   4. In Vivo Cytogenetics in mice. Lot 32.

I. PHARMACOLOGY (Sponsor's labs unless otherwise indicated)

A. CNS (Behavioral):

1. Anxiolytic activity -

a. Conditioned Avoidance Response (CAR):

Animal	Route	CAR ED50 (mg/kg)	UER (escape inhibitions) ED50 (mg/kg)
Rats	i.p.	4.3	84.9
	i.p.	3.6	88.0
	p.o.	18.2	358
Fasted female	p.o.	13.7	---
Nonfasted rats	p.o.	29.5	---
Fasted male rats	p.o.	47.9	---
Nonfasted male rats	p.o.	45.9	---
Monkey	i.m.	2-16	---
Mouse	i.p.	36.7	120
	p.o.	71.3	311

b. Continuous Sidman Avoidance-rats
Dose-related activity at 1 to 4 mg/kg, i.p.

c. Amphetamine-Aggregation Stress-mice
Protection from 20 mg/kg s.c. dl-amphetamine toxicity with ED_{50} of 9.8 mg/kg s.c.

d. Inhibition of Aggressive Behavior-monkey
Buspirone showed dose-related activity from 20 to 160 mg/kg, p.o. Diazepam was active from 5 to 20 mg/kg p.o. In contrast to diazepam, hypoactivity was seen only with high doses of buspirone.

e. Foot Shock-Induced Fighting-mice
ED_{50} for diazepam was 3.4 mg/kg p.o. and for buspirone was 182 mg/kg p.o., for one mouse strain, and 80 mg/kg for another strain.

f. Conflict behavior-rat and
Buspirone was active at 5 mg/kg p.o. but not i.p. at this dose, whereas diazepam was effective at 5 mg/kg i.p. but not p.o. for milk reward. For water reward in thirsty rats, the minimum effective oral dose for buspirone was 1.0 mg/kg and for diazepam was 0.5 mg/kg.

g. Conflict behavior-monkey

Buspirone was active at doses between 0.5-3.0 mg/kg i.m. and 5 mg/kg p.o., as was diazepam. Anticonflict behavior was generally seen on the day after treatment and lasted up to 2 weeks. These findings are compatable with the idea of an active metabolite.

h. Effect on Social Interaction-rats

Acute effects (0.25-2.5 mg/kg) purported to be "partial anxiolytic"-like effects similar to presynaptically-acting doses of piribedil. Chronic administration (5 days) of buspirone did not change behavior as opposed to diazepam which increased social interactions throughout. This study is from the and is not very convincing.

2. Sedative Activity

a. Spontaneous motility (Sponsors labs and

Doses of buspirone and diazepam necessary to reduce motility by 0.3 log units were:

Buspirone (mg/kg)		Diazepam (mg/kg)	
Mouse	Rat	Mouse	Rat
33 i.p.	40 i.p.	---	---
92 p.o.	66 p.o.	7 p.o.	25 p.o.

With photocell activity meters, a reduction in motility was seen with 16 mg/kg i.p. of buspirone.

b. Hexobarbital Potentiation-(Sponsors labs and

With a subhypnotic dose of hexobarbital (40 mg/kg, i.p.) the doses necessary to induce loss of righting reflex in half the animals were:

Hexobarbital Potentiation ED_{50}s (mg/kg)

	Buspirone		Diazepam	
	Rat	Mouse	Rat	Mouse
p.o.	15.5	54.5	0.2	0.35
s.c.	---	26.6	---	0.31

Buspirone was also without significant effect when combined with pentobarbital or barbital.

c. Ethanol potentiation -
Similar to above, i.e. very little effect.

ED50s (mg/kg p.o.)

Buspirone		Diazepam	
Rat	Mouse	Rat	Mouse
47.3	62.8	1.1	1.0

3. Seizure Control

a. Anticonvulsant activity-
Buspirone showed little or no anticonvulsant activity up to 400 mg/kg p.o. against pentylenetetrazol, picrotoxin, bicuculline, strychnine or electroshock in the rat as opposed to diazepam, which did in all cases.

b. ECS Threshold
Diazepam increased ECS threshold by 15% at 40 mg/kg p.o. Apomorphine decreased threshold by 23% at 40 mg/kg p.o. Buspirone also decreased threshold but to a lesser degree (14% at 40 mg/kg p.o.).

4. Muscle Relaxant Activity

a. Motor incoordination (rotarod)

ED_{50} (mg/kg p.o.)

	Buspirone	Diazepam
Rats	24.5	12.3
Mice	255 (58 i.p.)	12.5

Male rats showed 100% performance failure for 2 hr at 40 mg/kg p.o., while 50% of female rats at the same dose were unable to perform after 48 hr at 20 mg/kg p.o.; 100% of females were unable to perform at 2 hr.

b. Muscle weakness - (Suspended on bar by front paws)

ED_{50} (mg/kg) p.o.)

	Buspirone	Diazepam
Mouse	184	1.6
Rat	400	13.6

5. Electrophysiologic Activity

a. EEG profile-rabbit, cat, rat
Buspirone was similar, though less potent, to methylphendiate and d-amphetamine and dissimilar to thioridazine and chlorpromazine in rabbit and cat at 0.5 mg/kg i.v. and s.c., respectively. At a higher dose (2 and 8 mg/kg, s.c.) in cats, buspirone resembled both the stimulants and the neuroleptics.

Zero-cross analysis EEG in the cat -
Orally administered buspirone was similar to apomorphine and piribedil, but not diazepam, thioridazine or methylphenidate in the cortex; similar to methylphenidate in amygdala; and similar to apomorphine only, in the hippocampus. In the rat, oral buspirone at low doses (5-10 mg/kg) was similar to apomorphine, piribedil and thioridazine while at high doses (20-40 mg/kg) buspirone was similar to methylphenidate.

b. Sleep-wakefulness-cat
At 3 mg/kg p.o. there was a decrease of REM sleep and a slight increase in wakefulness and non-REM sleep. 6 mg/kg, p.o., t.i.d. showed similar effects except for a decreased wakefulness. There was a rebound REM after drug withdrawal.

c. EEG and Evoked Potential Waveforms-cat
This complicated study in cats with 34 implanted electrodes performing a conditioned avoidance response was published in the _____ of the _____ The results contained some 30 tables and figures of extremely complex data, none of which appeared to be very meaningful to me regarding the pharmacology of buspirone. The only conclusion of the author regarding buspirone is that it may disrupt cortical function less drastically and of shorter duration than chlorpromazine.

d. Dopamine autoreceptors and neuronal activity (report from _____ and _____)
Using neurochemical and single unit recording techniques in rats, these authors showed that buspirone blocks both pre- and post-synaptic dopamine (DA) receptors. In this action, it is similar to neuroleptics. Buspirone, however, also blocked the inhibition of DA neurons induced by iontophoretically applied GABA, as well as DA-induced inhibition. The former action is exclusive to buspirone, as neuroleptics cause a selective blockade of DA-induced inhibition.

The authors could draw no conclusions as to the mechanism of anxiolytic effects of buspirone. Together with other studies, however, these results suggest to me that buspirone causes a rather selective inhibition of DA autoreceptors.

In similar studies by et. al., the dopamine antagonist properties of buspirone were confirmed. However, in vivo studies using apomorphine--induced stereotypy on turning behavior in unilateral nigral lesioned rats, indicated buspirone is only a very weak postsynaptic DA-receptor antagonist. High doses did not induce catalepsy as opposed to clinically effective antipsychotics.

f. Effects on spinal Reflexes-cat

Buspirone caused an increase in amplitude of the dorsal root reflex and the monosynaptic reflex. Doses were not provided in the report, however.

The authors suggest that buspirone may affect spinal reflex activity by suppressing pre-synaptic inhibitory mechanisms.

6. Miscellaneous

a. Antiemetic activity

Emesis induced in dogs by 0.5 mg/kg i.v. apomorphine was blocked by 5 mg/kg i.v. buspirone pretreatment, a relatively high dose.

b. Effect on Body Temperature

Buspirone induced a mild hypothermia - minus 3, 4, and 6°F in fasted rats after 10, 30 and 100 mg/kg p.o., respectively. Comparative hypothermia for these doses of chlorpromazine was 7, 13 and 18°F.

c. Analgesic Activity

Buspirone was ineffective in the phenylquinone-induced writhing test in mice at doses up to 40 mg/kg s.c.

d. Anti-apomorphine Activity

Apomorphine-induced hypermotility in mice was antagonized only by high doses of buspirone (32 mg/kg or greater, i.p.). Lower doses tended to potentiate the effects of apomorphine. Buspirone had similar effects on the other actions of apomorphine such as hypothermia and stereotypy. In rats, buspirone antagonized stereotypy at doses as low as 4 mg/kg, i.p., and had an oral ED_{50} of 28 mg/kg.

The authors could draw no conclusions as to the mechanism of anxiolytic effects of buspirone. Together with other studies, however, these results suggest to me that buspirone causes a rather selective inhibition of DA autoreceptors.

In similar studies by et. al., the dopamine antagonist properties of buspirone were confirmed. However, in vivo studies using apomorphine--induced stereotypy on turning behavior in unilateral nigral lesioned rats, indicated buspirone is only a very weak postsynaptic DA-receptor antagonist. High doses did not induce catalepsy as opposed to clinically effective antipsychotics.

f. Effects on spinal Reflexes-cat

Buspirone caused an increase in amplitude of the dorsal root reflex and the monosynaptic reflex. Doses were not provided in the report, however.

The authors suggest that buspirone may affect spinal reflex activity by suppressing pre-synaptic inhibitory mechanisms.

6. Miscellaneous

a. Antiemetic activity

Emesis induced in dogs by 0.5 mg/kg i.v. apomorphine was blocked by 5 mg/kg i.v. buspirone pretreatment, a relatively high dose.

b. Effect on Body Temperature

Buspirone induced a mild hypothermia - minus 3, 4, and 6°F in fasted rats after 10, 30 and 100 mg/kg p.o., respectively. Comparative hypothermia for these doses of chlorpromazine was 7, 13 and 18°F.

c. Analgesic Activity

Buspirone was ineffective in the phenylquinone-induced writhing test in mice at doses up to 40 mg/kg s.c.

d. Anti-apomorphine Activity

Apomorphine-induced hypermotility in mice was antagonized only by high doses of buspirone (32 mg/kg or greater, i.p.). Lower doses tended to potentiate the effects of apomorphine. Buspirone had similar effects on the other actions of apomorphine such as hypothermia and stereotypy. In rats, buspirone antagonized stereotypy at doses as low as 4 mg/kg, i.p., and had an oral ED_{50} of 28 mg/kg.

e. Catalepsy

Buspirone failed to induce catalepsy in rats at doses up to 32 mg/kg, i.p. and 200 mg/kg p.o. compared to chlorpromazine which had an ED_{50} of 4.1 mg/kg p.o.

Buspirone was found to reverse catalepsy induced by trifluoperazine in the rat with an ED_{50} of 3.6 mg/kg p.o. compared to apomorphine and scopolamine which had ED_{50}s of 4.6. mg/kg, s.c. and 2.5 mg/kg p.o., respectively.

A study from the in reports that buspirone (1 mg/kg, p.o.) could reverse catalepsy induced by haloperidol, cis-flupenthixol and Ro 4-1284 (which depletes neuronal DA. Thus, presynaptic DA stores are not necessary for this reversal.

Another important finding was that buspirone's effects on DA metabolism are 10 fold greater with s.c. compared to i.p. administration. No such differential of effects was found with catalepsy reversal. This suggests that buspirone's effects on DA metabolism require the presence of the parent compound, while catalepsy reversal does not. It should be mentioned here that the 1-PP metabolite of buspirone has anti-cataleptic effects.

In a report by co-authored by the issue of anticataleptic activity of buspirone was reviewed. A complex theoretical arguement is proposed which suggests mechanisms by which buspirone may antagonise neuroleptic-induced catalepsy.

This arguement incorporates electro-physiological data which demonstrates that buspirone increases impulse flow in nigro-striatal DA neurons. It appears that this increase is not due to a functional blockade of postsynaptic DA receptors, but may be due to an inhibition of GABA-mediated inhibition (which results in disinhibition) through an, as yet undemonstrated effect of buspirone at the chloride ion channel which is associated with the GABA receptor (buspirone has no affinity for the GABA receptor).

While as yet theoretical, this arguement is plausible and would help to explain some of buspirone's unusual effects.

B. Neurochemistry

1. Receptor Interactions

a. Benzodiazepine binding

, reports no displacement of ^{3}H-diazepam binding in vivo by 5 mg/kg, s.c. or 10 mg/kg, p.o. buspirone.

reports that buspirone concentrations of up to 100 uM had no effect on ^{3}H-diazepam binding in rat cerebral cortex. Chronic buspirone treatment (6 mg/kg, i.p. for 30 days) did not affect 5-HT_2, GABA, alpha$_1$, alpha$_2$, beta-adrenergic, or benzodiazepine receptor binding in rat brain cortex, cerebellum or hippocampus. Nor did this treatment affect the ability of GABA to enhance benzodiazepine binding. However, chronic buspirone did increase ^{3}H-muscimol binding to striatal GABA receptors but did not affect DA receptor binding in this same region. A replication of this same experiment failed to reproduce this 40% increase in K_d for muscimol binding. proposes a third study to settle the question.

Note: No mention of the study can be found in any of the sponsor's tables of contents or summaries!

Work performed at the sponsor's labs tested effects of buspirone on flunitrazepam and diazepam binding, GABA enhancement of flunitrazepam binding, and GABA effects on diazepam and muscimol binding, all in vitro. No effects were found at buspirone concentrations up to 100 uM.

b. Interaction with other receptor sites.

In addition to the Enna study, above, the sponsor performed binding studies in vitro on various amine receptors and found no significant activity. IC_{50}s were as follows:

BUSPIRONE INTERACTION WITH RECEPTOR SITES

Receptor Type	^{3}H-Ligand	Brain Region	IC_{50}(nM)
$alpha_1$	WB-4101	cortex	1047
$alpha_2$	clonidine	cortex	12,900
beta	dihydroalprenclol	cortex	100,000
muscarinic	QNB	hippocampus	292,000
glutamate	kainic acid	whole brain	100,000
glycine	strychnine	medulla/pons	706,000
H_1	pyrilamine	whole brain	1,783
H_2	cimetidine	whole brain	65,500
opiate	diprenorphine	midbrain	43,300
5-HT_1	5-hydroxytryptamine	midbrain	14,800
adenosine A_1	cyclohexyladenosine	whole brain	1,000,000
adenosine A_2	diethylphenylxanthine	whole brain	651,000
dopamine agonist	N-n-propylnorapomorphine	whole brain	151
dopamine antagonist	spiperone	striatum	245

In contrast to the in vitro data, repeated treatment of rats with buspirone (2 mg/kg, p.o., t.i.d. for 28 days) resulted in a significant decrease in 5-HT_2 and beta-adrenergic receptor binding. No changes were seen in DA or GABA binding. Similar treatment with 0.5 mg/kg trifluoperazine, however, caused a significant increase in DA and 5-HT_2 binding with no change in GABA or beta receptor binding.

Thus, the changes seen with chronic treatment resemble those seen with antidepressants rather than anxiolytics or neuroleptics.

Another study by the sponsor showed no effect of 1000 nm buspirone, promethazine or diazepam on ^{3}H-muscimol binding in rat cerebellar or cerebral cortex.

c. Dopamine (DA) Receptor Activity

1. J

The following narrative is the above author's discription of the experiments performed in his laboratory:

"In the calf striatum, buspirone displaced [^{3}H] dopamine with high affinity (K_I = 170 nM) from 25 percent of the binding sites and not at all (K_I greater than 1 mM) from the remaining sites. This has never been observed before with any dopaminergic agent. Buspirone displaced [^{3}H] apomorphine with high affinity (K_I = 140 nM) from 47 percent of the binding sites and, again, not at all from the remaining sites. The difference in the proportion of sites between [^{3}H] dopamine and [^{3}H] apomorphine is the result of these ligands labeling different proportions of the various binding sites present. It has been found that N-n-propylnorapomorphine (NPA) tends to act more as an antagonist than dopamine or apomorphine (1]). In contrast to its inability to displace [^{3}H] dopamine and [^{3}H] apomorphine binding completely, buspirone always displaced [^{3}H] antagonists completely. Thus, in most instances, [^{3}H] NPA was displaced from 67 percent of the binding sites with high affinity (K_I = 90 nM) and from the rest of the sites at lower affinity (K_I = 1-4 uM). Guanyl nucleotides decrease the affinity of dopaminergic agonists for binding sites labeled with [^{3}H] antagonists. In the presence of guanylyl imidodiphosphate (GMP-PNP), the number of low affinity sites labeled by the antagonist [^{3}H] domperidone was increased from 14 to 24 percent. Had this experiment been analyzed using a one-site model, a change in K_I from 194 to 440 nM would have been seen. Similar shifts have been reported for buspirone (3,4). Such a shift was also noted in a replication of this experiment. The increase inproportion of low affinity sites and the decrease in K_I for buspirone at the high affinity sites in the presence of guanyl nucleotides was also seen in experiments using the antagonist [^{3}H] spiperone. In the rat striatum buspirone displaced [^{3}H] dopamine from 60 percent of the binding sites with high affinity (K_I = 30 nM) and from the remainder of the sites with lower affinity (K_I = 20 uM); however, in two experiments buspirone failed to displace all of the ligand in a fashion similar to that seen in the bovine striatum. Guanyl nucleotides induced a loss of affinity in this tissue, as in the calf, when [^{3}H] domperidone was used to label binding sites. Buspirone showed a slight shift in the inhibition of [^{3}H] spiperone binding to membranes from the bovine anterior pituitary in the presence of guanyl nucleotides."

Thus, while buspirone clearly is interacting in vitro with DA receptors, pre- and postsynaptically, the nature of the interactions are unique to this compound and do not lend themselves to simple analyses. In an addendum, Dr. refers to the high affinity site as the D_2 receptor and the low affinity site as D_3.

2. 5-HT Sensitive Adenylate Cyclase.
A report from a ' at indicated that buspirone is active in a liver fluke assay for 5-HT sensitive adenylate cyclase with an ED_{50} of 50 uM. While this does not appear to be a very high affinity, the author (and indeed the sponsor) seems rather excited about it. A full report on this phenomenon was not included in the submission.

2. Neurotransmitter Interactions

a. Noradrenergic Systems
Two reports from
indicate that 2.5 mg/kg, p.o. buspirone or higher in rats caused a decrease in striatal norepinephine (NE) for 120 min and 5 mg/kg p.o. causes a decrease in hippocampal NE. Increases were seen in MHPG in rest of brain at 120 min and beyond at doses of 10 mg/kg and above.

Chronic treatment with buspirone (40 mg/kg, p.o.for 7 days) did not alter basal NE or MHPG levels 24 hr after, nor did they affect the acute response to buspirone. Chronic haloperidol decreased basal MHPG levels and abolished the ability of haloperidol, but not of buspirone, to elevate MHPG acutely.

Acute i.p. administration of 50 mg/kg buspirone, but not 5 mg/kg, reduced NE levels 75% at 1 hr. and 26% at 4 hrs.

Note: The large doses employed in these studies may not be relevant to buspirone's clinical anxiolytic activity.

b. Dopaminergic (DA) Systems
Sponsor reports that 50 mg/kg i.p. buspirone, but not 5 mg/kg, causes a decrease in rat brain DA levels of 61% at 1 hr. and 22% at 4 hrs.
Again, effects at these high doses are of questionable relevance.

eports that buspirone produces equivocal effects on DA systems after p.o. dosing. In some experiments doses of 10 to 40 mg/kg buspirone resulted in decreased striatal DA but not in others. Buspirone (2.5 to 50mg/kg,p.o.) did elevate HVA and DOPAC which would be an indication of increased DA turnover. However, 3-methoxytyramine (3-MT) was not increased by buspirone; clozapine also lacked this effect on 3-MT.

Buspirone displaced ^{3}H-spiperone in striatal homogenates with a K_I of 90 nM. Buspirone also inhibited basal and DA-stimulated adenylate cyclase in vitro but did not displace trifluoperazine bound in vitro to bovine calmodulin at concentrations up to 100 uM. Chronic treatment with buspirone did not alter striatal DA, HVA or DOPAC nor did it alter the acute effects of buspirone, haloperidol or clozapine.

Chronic haloperidol, however, produced a decrease in responsiveness of HVA and DOPAC after acute haloperidol or buspirone. Chronic haloperidol (1 mg/kg twice daily for 25 days) but not clozapine or buspirone (20 mg/kg twice daily for 25 days) increased the number of ^{3}H-spiperone binding sites.

A study by [redacted] at [redacted] utilizing a decarboxylase inhibitor prior to drug treatment and measuring accumulation of DOPA and 5-HTP, was performed in order to get an indication of monoamine turnover. 10 mg/kg buspirone i.p. produced at least a 2 fold increase in DOPA in both dopaminergic and noradrenergic areas of rat brain. 5-HTP was uniformly decreased by buspirone. Corresponding changes were seen in DOPAC, HVA and 5-HIAA levels with no change in DA, 5-HT or NE levels.

The behavioral effects at this dose (stiff tail, flat body posture, forepaw extension and treading and abducted hindlimbs) suggested to the above authors that buspirone may enhance 5-HT receptor activation.

While no other experiments were performed, the authors conclude that buspirone may cause a blockade of DA and alpha-adrenergic receptors and a stimulation of 5-HT receptors. A nasty decision in my estimation.

The sponsor performed similar studies on DOPA accumulation after decarboxylose inhibition and blockade of impulse flow with large doses of gamma-butyrolactone. The results were very erratic as both increases and decreases were seen, depending on the pretreatment drugs, doses, and time intervals. No conclusions can be drawn from these data.

c. Serotonin Systems

In addition to the [redacted] study above, the sponsor reports that acute buspirone at 50 mg/kg i.p. but not 5 mg/kg i.p. causes a 17% decrease in brain 5-HT at 1 hr. (Hardly relevant to the therapeutic range).

reports that buspirone (2.5 to 80 mg/kg, p.o.) had no effect on 5-HIAA in rat striatum but at 40 mg/kg decreased 5-HIAA in the hippocampus. Chronic treatment did not alter the acute effects.

(The relevance of any of these effects is doubtful.)

As the sponsor was unable to replicate the "serotonin syndrone" described by they attempted another study using 5, 7 DHT-lesioned animals. This model should be more sensitive to 5-HT agonists. Buspirone had no serotonin-like effects other than flat body posture at 10 mg/kg, i.p. The lesioned animals also showed rapid sniffing and chewing movements.

d. Cholinergic Systems

reports that buspirone was essentially devoid of activity in vitro in the inhibition of ^{3}H-dexetimide binding to muscarinic receptors in rat hippocampus (IC_{50}=60uM). Incubation with 10uM buspirone yielded no effects on choline acetyltransferase or acetylcholinesterase activities in striatal homogenates. Oral administration of doses from 2.5 to 40 mg/kg to female rats resulted in a lowered concentration of Ach in the striata. Lesser effects were found in males and no effects were found in hippocampus, rest of hemispheres or brain stem. The largest effect occurred within 15 min. Apomorphine had the opposite effect, i.e. it produced an increase in striatal Ach.

e. Miscellaneous.

Buspirone had no relevant effects on phosphodiesterase or its activation by calmodulin. Buspirone did not affect the activity of tyrosine hydroxylase or the effects of gamma-butyrolactone on this enzyme.

C. Cardiovascular, Respiratory and Renal Systems

1. Acute cardiovascular and respiratory toxicity in dogs.

Anesthetized dogs (N=20) received i.v. infusions of 0.5, 1.0 or 2.0 mg/kg/min of buspirone. Lethal actions included respiratory arrest, which in all cases preceded cardiovascular collapse. The former occurred at cumulative doses of 75 and 87 mg/kg when infused at 1 and 2 mg/kg/min, respectively, in barbital treated dogs, and the latter at similar dosages. Death occurred at about 125 to 130 mg/kg. In alpha-chloralose anesthetized dogs, about 120 mg/kg was required for respiratory arrest, 149 for cardiovascular collapse, and 166 for death.

Major cardiovascular effects were hypotension and decrease in left ventricular dp/dt. LVEDP was slightly increased while heart rate was slightly decreased. Cardiac index, stroke work and left ventricular work remained near normal. Respiratory rate and depth were increased by buspirone initially, followed by a reduction in depth (below baseline at lower dose only). Differences in rate of buspirone administration did not significantly alter cumulative toxic dose. Effects of i.v. chlorpromazine were qualitatively and quantitatively similar to buspirone except for greater hypotensive effects by chlorpromazine.

2. Hemodynamics

a. Dog-
Mongrel dogs were anesthetized with pentobarbital and either barbital or chloralose for intact or stellate ganglion exposed preparations. Sponsors Table 3, page 4349 is shown below:

Cumulative hemodynamic effects of buspirone measured 30 min after administration of indicated doses (mg/kg) to 8 anesthtized dogs.

Parameter	Control	0.03	0.03	3
			% Change	
MABP (mmHg)	106±4	0±1[a]	-3±3	5±5
Aortic Blood Flow (L/min)	2.24±0.15	-3±2	-20±3	-22±3
Total Peripheral Resistance (mmHg/L/min)	49±4	3±2	23±6	36±8
Right Ventricular Contractile Force(g)	97±3	-3±2	-16±3	-18±3
Heart Rate(bpm)	139±6	-2±1	-10±3	-14±3
Left Ventricular dp/dt (mmHg/sec)	2394±135	1±3	-18±5	-21±2

[a] mean ± sem

Electrical stimulation of the right stellate ganglion elicited a frequency dependent increase in heart rate which was unaffected by buspirone at up to 3 mg/kg, whereas apomorphine caused a progressive right shift (0.03-0.3 mg/kg).

b. Rat -

Conscious normotensive and DOCA-salt hypertensive rats experienced a decrease in heart rate and blood pressure with high doses of buspirone (30-100 mg/kg, p.o.). In anesthetized rats, i.v. buspirone (0.3 and 3.0 mg/kg) caused a transient pressor response accompanied by a sustained bradycardia. Bolus injections in anesthetized, ganglion-blocked rats caused a dose-dependent (0.3 to 10 mg/kg i.v.) increase in blood pressure which was antagonized by phentolamine and prazosin equally; as opposed to apomorphine which was only antagonized by phentolamine.

This may indicate some alpha$_1$-agonist activity.

3. Water and Electrolyte Excretion

a. Rat -

3 to 100 mg/kg p.o. buspirone given to volume loaded, conscious rats was diuretic and natriuretic. The maximum response was at 30 mg/kg when urine volume increased by about 150% and sodium excretion was doubled.

b. Mouse -

P.O. doses from 0.1 to 1.0 mg/kg tended to increase water and electrolyte excretion (significant only at 0.3) in conscious mice while doses from 3 to 100 mg/kg caused significant dose-related (25-60% decrease) antidiuresis and antinatriuresis.

c. Dog -

In anesthetized dogs, buspirone (3 mg/kg, i.v.) caused significant elevations of urinary volume and chloride excretion. Greater changes were seen at 10 mg/kg. Blood pressure and heart rate tended to be decreased at these times. Oral doses (1.0 to 10 mg/kg) in conscious dogs caused no significant changes. Constant infusion of buspirone (9.7 ug/min.) into the left renal artery produced no changes in water or electrolyte excretion, but mean blood pressure and renal resistance in the infused kidney were reduced significantly.

D. Smooth Muscle and Autonomic Activity

1. Alpha-adrenergic activity -

The IC_{50} for buspirone on NE-induced contraction of rat seminal vesicle was 10,000 ng/ml.

The potency of buspirone to protect against epinephrine-induced lethality in mice was 0.032 times that of phentolamine. Buspirone also had no activity in the cat nictitating membrane assay.

2. Anticholinergic activity

Buspirone did not protect against physostigmine lethality in mice at doses up to 400 mg/kg, p.o. An IC_{50} of 292/uM for ^{3}H-QNB displacement also indicates a lack of antimuscarinic activity.

3.Isolated Smooth Muscle

Buspirone showed very weak direct muscle relaxant activity as well as a weak antagonism of histamine and 5-HT in rabbit ileum, guinea pig ileum, rat uterus, guinea pig trachea and rat seminal vesicle preparations. There was no relevant activity against alpha- or beta-adrenergic, cholinergic or ganglionic stimulation or on the activity of the duodenum or uterus.

E.Endocrine Actions

1. Gonadotropin-Induced Ovulation

Female rats were treated with pregnant mare serum (PMS) followed by buspirone. The presence, number and condition of ova in the oviducts showed suppressive effects by buspirone only at 50-90 mg/kg.

2. Uterotopic activity

Rats treated with buspirone and/or estrone for 3 days showed no effect from buspirone on the uterus at doses up to 160 mg/kg p.o.

3. Prolactin levels

Doses of 0.5 to 50 mg/kg, i.p. buspirone caused a dose-related increase in plasma prolactin in male rats. These effects were additive with alpha-methyltyrosine and gamma-butyrolactone. In vitro buspirone (10^{-6} M) had no effect by itself on the release of prolactin from rat pituitary glands but blocked the inhibitory action of DA, as did 10^{-7} M haloperidol.

D. Miscellaneous Actions

1. Local anesthetic activity-

Buspirone was 0.17 and 0.34 times as potent as xylocaine in the rabbit eye and guinea pig skin, respectively. It did not irritate rabbit eye at 2% but did irritate guinea pig skin at that concentration.

2. Metabolic responses-

At 15 and 30 mg/kg i.p., buspirone did not elicit hyperglycemic or hyperlacticacidemic responses. 20 mg/kg buspirone tended to reduce the hyperglycemic response and increase the lactate response to epinephrine.

3. Isoloated Rabbit ear artery
   Buspirone decreased the amplitude of response (increased perfusion pressure) to electrical stimulation. In contrast to DA and apomorphine, it did so only at doses which caused direct vasoconstriction. Haloperidol reduced the effects of all 3 drugs.

4. Ethanol preference in mice
   There was a dose-related suppression of ethanol preferance (administered in drinking water) with p.o. doses of 25, 50 and 75 mg/kg buspirone and at 10 mg/kg only with diazepam. At these dosages, the relevance of these findings is dubious.

II. PHARMACOKINETICS

Note: Three different forms of labeled buspirone have been used for pharmacokinetic studies. Initially, a random tritium label was used and later a 2-pyrimidyl-^{14}C and also a 1,3 $^{15}N_2$ pyrimidyl label was used for identification of metabolites.

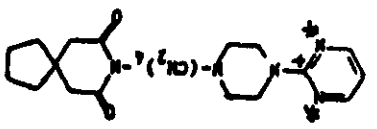


Figure 1. Structure of buspirone, 1, indicating position of ^{14}C (+) and ^{15}N (*) labels.

Analytical Methods
Three different assays have been used for quantification of buspirone: GLC, HPLC, and RIA. Only the RIA is sufficiently sensitive for measuring tissue, urine and plasma levels of buspirone (4 pg or greater).

A. Absorption

1. Rat

   Isoloated rat stomach and small intestine was ligated and 0.1 mg ^{3}H-buspirone introduced. No significant absorption occurred from the stomach but 55% of the label was absorbed through the small intestine within 40 min.

Buspirone mixed with the diet at 19, 32 and 64 mg/kg produced blood levels of 3-20 ng/ml and 2-15 ng/ml at 1 and 3 hr, respectively, at the high dose. Blood levels were unmeasurable by GLC (less than 2 ng/ml) at the lower doses.

2. Monkey

Oral doses of ^{15}N-buspirone were compared with i.v. doses of ^{14}C-buspirone in one study. In aother study, monkeys received 5 mg/kg ^{3}H-buspirone, p.o. verses i.v. Maximum plasma levels of unchanged drug occurred at approximately 2 hr and the majority of radioactivity was recovered from the urine. While bioavailability appeared to be low (1-12%) due to "presystemic elimination", total absorption appeared to be good. Oral pretreatment for one week did not affect disposition in monkeys.

B. Distribution

Tissue distribution in the rat after a 10 mg/kg oral dose of $^{15}N/^{14}C$-buspirone is shown in the following table prepared by Mead Johnson.

Tissue Distribution of Radiolabel from ^{14}C-Buspirone[1]

Tissue	Time 1 hr	3 hr	6 hr	24 hr	72 hr
Plasma	0.456±0.32	0.620±0.48	0.462±0.58	0.015±.001	0.003±0.000
Adrenals	0.015±0.002	0.008±0.000	0.005±0.001	0.002±0.000	0.000±0.000
Brain	0.173±0.024	0.067±0.006	0.030±0.006	0.005±0.001	0.002±0.000
Liver	8.37±0.76	3.82±0.29	2.56±0.33	0.938±0.037	0.282±0.098
Kidney	1.08±0.14	0.498±0.024	0.488±0.03	0.046±0.002	0.019±0.004
Heart	0.112±0.029	0.046±0.001	0.021±0.003	0.004±0.000	0.002±0.000
Spleen	0.147±0.022	0.039±0.010	0.019±0.004	0.002±0.000	0.000±0.000
Lung	0.229±0.008	0.092±0.011	0.039±0.007	0.004±0.000	0.002±0.000
Testes	0.298±0.067	0.201±0.034	0.096±0.015	0.018±0.001	0.009±0.002
Skeletal Muscle[b]	0.124±0.034	0.069±0.026	0.043±0.018	0.006±0.001	0.004±0.002
Stomach[c]	0.70±6.8	0.315±0.12	0.138±0.058	0.021±0.013	0.013±0.002
Sm. Intestine[c]	38.0±4.6	25.5±7.1	18.0±4.6	1.06±0.11	0.064±0.028
Lg. Intestine[c]	0.925±0.15	16.8±11	23.6±6.8	3.51±3.3	0.116±0.082
Fat[b]	0.047±0.012	0.030±0.036	0.010±0.007	0.002±0.001	0.000±0.000
Skin	3.50±0.52	1.59±1.0	1.06±0.40	0.503±0.41	0.617±0.28
Carcass	12.5±2.0	7.32±0.64	0.077±0.024	0.400±0.060	0.315±0.016

[a]Values are percent of dose per whole tissue ±SE, n = 3.
[b]Values are percent of dose per gram of tissue ±SE, n = 3.
[c]Including contents.

Large amounts of label found in small intestine were thought to be partly due to biliary excretion.

Preloading with 48 or 160 mg/kg buspirone, p.o., for 3 or 24 days had no significant effect on distribution in the rat.

C. Metabolism

1. Rat-

Metabolism accounts for all the elimination in rat as no detectable amounts of unchanged drug are excreted in urine or bile after a 10 mg/kg oral dose. Approximately half of the urinary excretion over 24 hr (12% of total dose) appeared to be glucuronate or sulfate conjugates. Approximately 30% of the total collected from bile at 0-6 hr, (37% of total dose of radioactivity) was conjugated.

Buspirone is extensively metabolized by hydroxylation and oxidative cleavage. In urine, approximately half (7% total dose) of the extractable radioactivity was a monohydroxy derivative of buspirone in which the hydroxyl group is on the azaspirodecane moiety (see 3 in sponsor's figure on next page). Synthesis of 3a and 3b showed them not to be the above derivatives.

The remaining metabolites consisted of compounds which are presumably further oxidation products of 3 (i.e. 6, 7, 8, and 9). In bile, 75% (37% dose) were glucuronide conjugates of the 5-hydroxy derivative of buspirone, 2, and two isomeric dihydroxy derivatives of buspirone (4 and 5). The metabolic scheme proposed is shown in the sponsor's figure on next page.

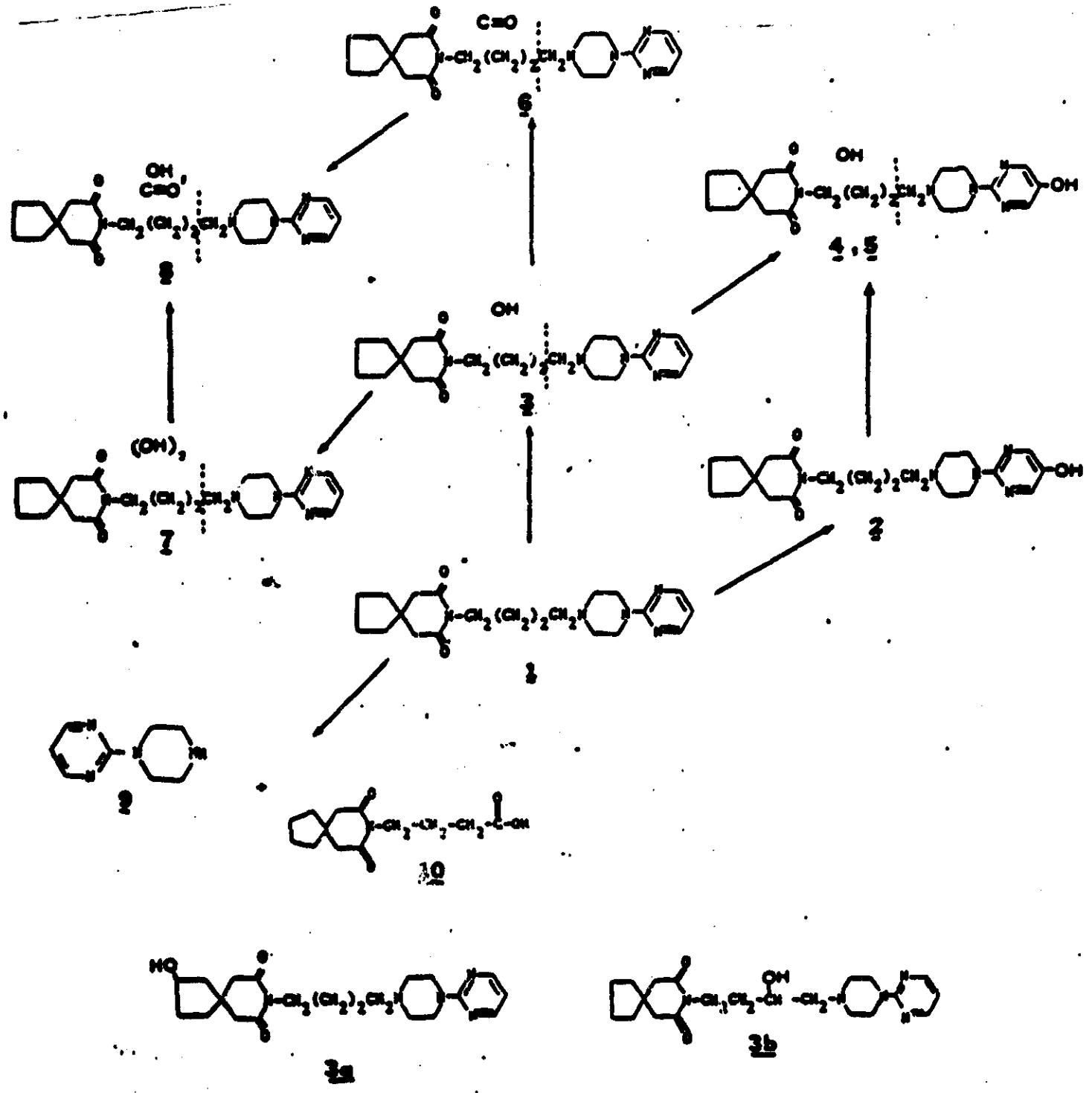


Figure 3.

Proposed Metabolic Scheme for Buspirone

The primary metabolites in rat in order of prevalence are: 3, 2 (the 5-hydroxy derivative of buspirone), and the two isomeric dihydroxy derivatives, 4 and 5.

Three reports from [redacted] are concerned with the metabolism and pharmacokinetics of buspirone in the rat. These studies are potentially of great importance for they are concerned with metabolites of buspirone in plasma and brain. Relevant findings are summarized below:

1. Plasma half-life of buspirone declined biexponentially after i.v. administration of 10 mg/kg; the first being 2.7 min and the second 30 min. In this same experiment, the half-life of a major metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP, MJ 13653), was 120 min. The Cmax of 1-PP was 1.34±0.30 nM/ml at about 90 min. The AUC for 1-PP and for buspirone was 336 nM/ml/min and 481 nM/ml/min, respectively.

2. After oral administration of 10 mg/kg buspirone, no parent drug could be detected in rat plasma (less than 1 nM/ml), whereas the half-life and AUC for 1-PP were comparable to that observed following i.v. administration of buspirone or i.v. administration of 1-PP.

   After 100 mg/kg p.o. buspirone, the plasma AUC for parent and 1-PP were 929 nM/ml/min and 4024 nM/ml/min, respectively. The apparent half-lives were much longer than for the 10 mg/kg dose, (137 min for buspirone and 368 min for 1-PP), suggesting dose-dependent pharmacokinetics.

3. Buspirone and 1-PP were both found in higher concentrations in the brain than in plasma after i.v. or oral administration of buspirone.

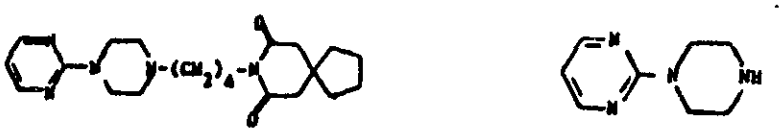
4. After 10 mg/kg p.o. buspirone, plasma concentrations of 1-PP peaked within 15 min and disappeared with a half-life of 143 min. Maximum brain concentrations of 1-PP were about 5 times higher (8.5 nM/ml) than plasma max and occurred at about 30 min. The half-life of 1-PP in brain was similar to that in plasma while the AUC of 1-PP in brain was about five times the plasma AUC.

5. 1-PP is reported to have anticonflict activity, and is capable of reversing neuroleptic-induced catelepsy.

6. 1-PP does not affect dopamine receptor binding.

7. While 1-PP does not displace ^{3}H-diazepam binding in vitro, it does enhance ^{3}H-GABA binding in vitro, as does buspirone. While buspirone enhances ^{3}H-diazepam binding in vivo, 1-PP has not yet been tested in vivo.

The structure of 1-PP is shown below in comparison with buspirone.



Buspirone

The significance of these reports is obvious: [illegible]se of buspirone which has anticonflict activity in rats (1-3 mg/kg, p.o.) results in unmeasurable plasma and brain levels of the parent compound, while an active metabolite (1-PP) does reach significant levels and has a much longer half-life. Since 1-PP has no effect on dopamine systems and the minute amount of buspirone present would be unlikely to have significant effects, the potential for tardive dyskinesia in humans (if the pharmacokinetics are similar) would appear to be unlikely. The sponsor has made little mention of these studies by [redacted] and has not performed any studies on plasma metabolites in humans or animals to my knowledge. Further studies of buspirone metabolism could clearly throw a whole new light on the neuropharmacology of this compound.

In another study from the sponsor's labs, the 5-OH metabolite was tested in comparison with buspirone on the EEG of cats. The metabolite was found to have a quantitatively similar profile to buspirone at oral doses between 1.25 and 20 mg/kg.

I recommend that the sponsor further characterize these and other metabolites, especially 1-PP. Of special interest are plasma levels and half-life in man.

2. Monkey-

Metabolites found in monkey urine after a 2.5 mg/kg i.v. dose of buspirone were similar to the rat. Relative amounts of buspirone derivatives according to the previously given figure are:

Compound	Structure	Relative Amount (%) of total Urinary Activity
M1	6	11
M2	6	14
M3	3	28
M4	7,8	18
M5	3	12
M6	9	17

D. Excretion

1. Rat -

Following 5 mg/kg oral administration of ^{3}H-buspirone to 6 male rats, urinary excretion of radioactivity accounted for 37-49% of the dose while 30-39% was recovered in the feces. In another study, 10 mg/kg ^{14}C-buspirone was given orally to 7 male rats and urinary and fecal excretion accounted for 39% and 54% of the dose, respectively.

2. Monkey -

Urinary label recovered accounted for 59-67% of a 2.5 mg/kg i.v. dose coupled with a 25 mg/kg oral, unlabeled dose. Fecal recovery was 33%. Buspirone elimination half-life in males ranged from 1.5 to 2.4 hr and in females from 3.4 to 3.8 hr. Similar differences in elimination were seen in half-life of total radioactivity.

After a 5 mg/kg dose, 52% was recovered from urine and 15% from feces with oral administration, and 58% and 8% with i.v., respectively over a period of 168 hr.

Comments on pharmacokinetics:

This section of the NDA was poorly writted and organised. Following a telephone complaint to the sponsor, a summary of the pharmacokinetics section along with a revised and more complete table of contents for this and other sections, was sent to me.(June 13, 1983). Unfortunately, it was still not comprehensive.

III. TOXICOLOGY

Note: In this section, the abreviations, HDM, MDF, LDM, etc., refer to high/medium/low dose in male/female animals.

A. Acute Toxicology (Sponsor's table):

Species	Sex	Dose Route	LD_{50} (95% Confidence Interval) mg/kg
Rat (Adult) Sprague-Dawley	Males	Oral	265 (174-404)
Rat (Adult)	Males/Females	Oral	196 (152-252)
Rat (Newborn)	Males/Females	Oral	415 (332-520)
Mouse	Males	Oral	665 (529-811)
Dog	Males/Females	Oral	586 (371-925)
Monkey	Males/Females	Oral	356 (302-420)
Rat	Males/Females	Intraperitoneal	136 (122-152)
Mouse	Males	Intraperitoneal	164 (145-185)
Mouse	Males	Intravenous	73.3 (66.6-80.6)
Monkey	Males/Females	Intravenous	54.3 (47.6-61.9)
Dog	Females	Intravenous Infusion	125.3 mg/kg (lowest lethal dose - infused at 80 mg/kg/hr : 30.8 ml/hr)

There appears to be greater toxicity in female rats. This apparent difference was not tested specifically in any species, however.

In all species, death was preceded by clonic convulsions and profuse salivation.

B. Rangefinding Studies-

1. Rat-

Methods:

3 groups of 5 males and 5 females were began on doses of 37.5, 75 and 150 mg/kg/day buspirone, in the diet. Dose levels were raised (doubled) every 2 weeks until the maximum tolerated dose was obtained.

Mortality:
None

Weight:
During the first two weeks, all treated groups gained less weight than controls. Females receiving 150 mg/kg lost weight during this period. Food palatability was probably reduced at this dose and above. Food intake and weight gain were reduced in proportion to dose increase, with weight loss occurring throughout the 300 and 600 mg/kg feeding.

Organ Weights:
Increased relative liver weights in HDF; decreased absolute and relative spleen weights in HDF.

Histopathology:
Slight to moderate decrease in cellularity of bone marrow in HDF and HDM. Spleens were also slightly atrophied in 9/10 HD animals. Sponsor suggests these changes are related to poor nutritional condition.

Other changes appeared to be spontaneous.

2. Mouse -

Methods:
Two M and 2 F Swiss mice/group received 100, 160, and 250 mg/kg/day buspirone mixed with chow for 6 weeks At the 4 week point, the LD was raised to 316 mg/kg/day.

Results:
There were no significant changes reported for behavior, food consumption or body weight.

3. Dog -

Methods:
One M and 1 F beagle dogs/group received 73, 110 and 146 mg/kg/day buspirone (by capsule after feeding) for 14 days.

Results:
Throughout the study, convulsions, tremors, ataxia, hypoactivity and hyporeactivity were seen in almost all dogs. Hostility was also seen in both MD dogs. Emesis occurred only once, in the HDF. Both HD dogs died after the fifth dose following convulsions. The MDM died on day 11, possibly due to gastric dilitation.
All dogs lost weight during week 1 and all but the LDF lost more during week 2.

Organ weight analysis and gross necropsy findings were not remarkable, partly due to the small N.

4. Monkey -

Methods:

One M and 1 F rhesus monkeys/group received busprione- 100 or 200 mg/kg, or chlorpromazine (CPZ)- 25 or 50 mg/kg, by gavage.

Results:

In the first week all but LDM lost weight. In the 2nd week only the HDM (busp) lost weight. The HD animals exhibited decreased activity, ataxia and incoordination. Catatonia was observed in one 100 mg buspirone monkey once, as well as in both CPZ monkeys.

C. Subchronic

1. Rat - 3 month study

The following is the sponsor's summary of the methods:

"The subchronic toxicity of buspirone was determined during a 3 month study in the rat in which the drug was provided in the diet. Groups of 15 male and 15 female CD rats approximately 45 days of age and weighing approximately 115-140 grams were treated with diets (meal type) to provide 0, 50, 100 or 200 mg/kg/day of buspirone. All rats were examined daily for general health status, weighed weekly and examined for physical changes and subtle toxic signs during weeks 2, 3, 4, 5, 9 and 13. Food consumption values were determined on a weekly basis. Hematologic parameters consisting of packed cell volumes, hemoglobin concentration, RBC, WBC and differential counts were measured during weeks 5, 9 and at the end of the study on 10 male and 10 female rats from each dose group. The serum chemistry measurements for Na, K, Cl, CO_2 content, total protein, albumin, glucose, urea nitrogen, alkaline phasphatase, SGPT, total bilirubin and total cholesterol were determined at the end of the study using terminal blood samples. Statistical analyses of body weights, food consumption, hematology, serum chemistries and organ weights were done using Dunnett's test.

The animals were fasted and sacrificed during the 14th week of this study. The following organs were weighed at necropsy; adrenals, gonads, spleen, heart, kidneys, brain, liver and pituitary, while the thyroid was weighed after fixation. A complete gross pathologic examination of tissues was performed on all animals. A histopathologic evaluation was performed on a complete set of tissues for 10 males and 10 females in the control group and the 200 mg/kg/day dose group. Only suspected target organs were microscopically examined in the 50 and 100 mg/kg/day dose groups using 10 males and 10 females per group."

Results:

Mortality -
2 F and 1 M of CPZ group (died during blood sampling); 1 MDM week 12 (cause of death unknown).

Observations -
No drug-related effects.

Food Intake/Weight Gain -
M and F of HD and CPZ groups weighted less from week 1 on. By end of study, all treated males were lighter. Decreases occurred primarily during the first 5 weeks. In contrast, there appeared to be an increased food intake in proportion to dose which was significant in HD animals.

Note: Could this be due to food spillage as in rat 1 yr interim study?

Hematology -
week 5 - Decrease in PCV and hemoglobin in HDF. Increase total leukocytes in HDM. The MD groups had some tendencies as above but of less magnitude.

week 9 - Slight but significant decrease in hemoglobin in HDM and HDF and in total RBC for HDM. Slight decreases in mean PCV and RBC for HDF and slight increase in WBC in MDM.

week 14 - Slight but significant decreases in mean hemaglobin and RBC in HDM and F. Slight decrease in PCV in HDM and in Hb and RBC for MDF. Leutocyte count increased significantly in HDM and slightly in MDM.

Blood Chemistry-
Statistically significant decreases in total protein and glucose in HDM and F; increased BUN in F. Two HDF and 7 HDM had high serum potassium levels. LD groups had lower total protein.

Organ Weights -
With higher doses of buspirone absolute weights of heart, kidney, spleen, thyroid and liver were decreased. There were no changes in relative weights.

Gross Pathology -
No treatment-related changes.

Histopathology -
No treatment-related changes.

2. Monkey - 3 month study-

Sponsors statement of methods:

"The subchronic toxicity of buspirone was evaluated in the monkey during a 90 day study in which the drug was given orally as a solution. Groups of 2 male and 2 female monkeys weighing between 1.6 to 3.0 kg were administered single, daily doses of 37.5, 75 or 150 mg/kg/day of buspirone. The control group received 1 ml/kg of distilled water. All animals were weighed weekly, examined for toxic signs daily and given a detailed physical examination prior to the study, after week 7 and 2 days prior to the end of the study. The physical included: an ophthalmologic exam by gross observation with a binocular loupe and fundus observations using an indirect ophthalmoscope (photographs of the optic disc were taken), EKG tracings of Lead II, indirect blood pressure measurements, rectal body temperatures, and visual observation and palpation of many organ systems. Hematology parameters consisting of packed cell volumes [PCV], hemoglobin concentrations [Hb], erythrocyte sedimentation rates [ESR], RBC, WBC, differential and reticulocyte counts in addition to serum chemistry measurements including NA, K, Cl, CO_2 content, total protein, albumin, urea nitrogen, alkaline phosphatase, SGPT, total bilirubin and total cholesterol were performed once pretest and during weeks 8 and 13 of this study. Platelet counts, plasma prothrombin times and activated partial thromboplastin times were measured once pretest and during week 12 or 13. Monkeys were treated with 4 mg of phencyclidine HCl to immobilize and ease handling during physical exams or bleeding procedures. Statistical analyses of body weights, hematology, serum chemistry and organ weight data were done using Dunnett's test, except for the male groups where the limited number of surviving animals precluded a valid statistical evaluation. The monkeys were fasted overnight and sacrificed on day 93 (females) or day 94 (males) of this study.

The following organs were weighed at necropsy: heart, liver, kidneys, spleen, adrenals, ovaries, testicles, brain, pituitary and thyroid/parathyroid. A complete gross pathologic examination of tissues was performed on all animals and a complete set of tissues was processed and examined microscopically for the control group and those animals given 150 mg/kg/day. Only suspected target organs were processed and examined microscopically at the 37.5 and 75 mg/kg/day dose levels."

Results:

Mortality-
Both MDM died during week 5 or 6. Sponsor claimed it to be related to dosing accidents. 1 HDM died week 11 - probably due to pneumonia.

Gross observations-
At the LD, occasional hypoactivity and one incidence each of tremor and salivation were seen. At higher doses, these symptoms were more frequent and severe and included chewing on the wrists and cage. In addition, catatonia was sometimes observed early on in the mid and HD groups. While CPZ-induced hypoactivity tended to decrease with time, buspirone-induced hypoactivity tended to increase with time. All side-effects were transient and disappeared before the next dosing.

Body Weight/Food consumption-
During the first week, treated animals gained less weight but were gaining normally by week 2.

Cardiovascular-
There were no meaningful changes in heart rate, blood pressure or EKG.

Opthalmology-
No compound-related effects.

Clinical Lab-
Slight decreases in LDM, HDM and HDF for PCV, Hb and RBC. There were no compound-related effects on coagulation or blood chemistry.

Gross Pathology-
A pale, cyst-like structure was found on the liver of one HDM. All other findings were probably incidental and of no consequence.

Organ Weights-
Increased absolute adrenal weight in females was dose-related; relative adrenal weight increased only in HDF. There was a decreased relative pituitary weight in LD animals and decreased relative and absolute weight in HD animals. There was a dose-related increase in absolute and relative kidney weight in females only.

Histopathology -
All findings were considered spontaneous.

D. CHRONIC TOXICITY

1. Rat - 1 yr interim (see under E.1.).

2. Monkey - 1 yr. study.

Sponsor's statement of methods:

"The chronic toxicopathologic effects of buspirone were characterized in the monkey during a 52 week study. Groups of 4 male and 4 female adult monkeys, weighing between 2 and 5 kg, were initially treated with either 35, 62, or 110 mg/kg/day orally in distilled water. The control groups received 1 ml/kg of distilled water and another received 12.5 mg/kg CPZ b.i.d. The dose levels were changed according to the following times during the study:

Low Dose	35 mg/kg/day	Dose Days 1-23
	25 mg/kg/day	Dose Day 24-Term.
Mid Dose	62 mg/kg/day	Doses Days 1-13
	31 mg/kg/twice daily	Dose Days 14-23
	25 mg/kg/twice daily	Dose Day 24-Term.
High Dose	110 mg/kg/day	Dose Days 1-2
	55 mg/kg/twice daily	Dose Days 3-23
	50 mg/kg/twice daily	Dose Day 24-Term.

Individual body weights were recorded weekly, behavioral and general health status were checked several times daily, physical examinations were performed once pretest and then at monthly intervals, ophthalmoscopic examinations including tonometry were performed once pretest and at 8, 24 and 50 weeks, and blood pressures and EKG (Leads II, AVR and AVL) were recorded once pretest and at 8, 24, and 50 weeks. Hematology measurements consisting of hematocrit, hemoglobin concentration, RBC, WBC and differential and reticulocyte counts and erythrocyte sedimentation rate were performed twice pretest and at weeks 5, 9, 17, 27, and the end of the study. Serum chemistry parameters determined at these same time intervals were glucose, urea nitrogen, SGPT, SGOT, alkaline phosphatase, CO_2 content, total protein, albumin, total bilirubin, total cholesterol, Na, K and Cl.

Clotting evaluation (prothrombin time, platelet count and activated partial thromboplastin time) and routine urinalyses were performed once during the prestudy interval and at 26 and 52 weeks. All survivors were sacrificed at the end of 52 weeks. A complete gross pathologic examination was performed. The liver, kidneys, adrenals, spleen, gonads, heart, thyroid/parathyroid, brain and pituitary were weighed. A complete set of tissues from the controls and high dose level were processed for histopathologic evaluation. Only target organs were examined for all animals at the low and mid dose levels. All unusual lesions described at the time of necropsy were examined histologically. All tissues from animals dying or sacrificed in extremis during this study were also examined microscopically."

Results:

Mortality -
Survivers were:

	M	F
Control	4/4	4/4
LD	3/4	4/4
MD	4/5	4/4
HD	3/7	2/5
CPZ	4/6	1/8

Observations -
During the first month, sedation was moderate in LD and marked in MD and HD and CPZ animals. After dosage reduction, the MD group showed only moderate and the LD only slight sedation. Intention tremors were seen in some LD animals during the first 2 months, and in all other monkeys for the duration. Chewing on the cage or wrist was seen in half the HD animals and CPZ group. An arousable prostration was also seen in most HD animals and an occasional lack of response to sound or pinch stimuli in MD and HD animals. Partial to total anorexia was noted more often in MD and HD animals than control or CPZ animals. Soft stools and/or diarrhea was more frequent in buspirone-treated animals; bloody diarrhea prior to death in 1MDM, 2HDM, 1HDF and in 1M and 2F CPZ animals.

Body Weight-
Surviving animals had similar body weights. Marked losses were seen in monkeys that died during study. No food consumption data were reported. The large variance in animal weights would obscure any effects that might have taken place on this parameter.

Physical and Ophthalmoscopic exams-
No changes were seen in tenometry readings or ophthalmoscope exams.

Blood Pressure-
Sponsor says no drug-related changes, but HD animals had significant elevations in systolic mean pressures at 8 and 24 weeks. Other groups and time points appeared to have a tendency to increase.

EKGs-
Only copies of tracings are provided. No tabular data expressing relevant parameters such as PR intervals ect., are given. Sponsor claims no drug related effects.

Hematology-
Some MD and HD animals showed lower Hb and Hct values throughout the study. No other abnormalities were seen.

Biochemistry-
Serum GOT and GPT were slightly higher in HD animals while alkaline phosphatase in MD and HD animals was generally lower. HD animals also had lower cholesterol levels.

Urinalysis-
No drug related changes.

Clotting Studies-
No changes.

Organ Weights-
Relative increases were seen in liver for HDM and HDF; heart in all buspirone-treated groups; adrenals in all males and HDF (CPZ females also). Decreased were seen in relative weights of testes and were dose-related.

Note: In most of the above data, no summary tables or group means were provided, thus making group comparisons very difficult.

Gross Pathology-

Only likely drug-related lesion was mucosal hemorrhage of the large intestine.

Histopathology-

Sponsor claims no effects but there appears to be some increase in focal cellular hypertrophy and congestion of the adrenal and cervical and mesenteric lymph nodes; an increase in hyaline deposits in females; congestion and inflammation in the stomach and the small and large intestine in HD animals; a dose-related increase in immature testes and focal tubular degeneration in female kidneys. Sponsor claims inflammatory findings in the G.I. tract were due to gastroenteritis, however, no evidence is presented which would demonstrate an infectious process, nor is there an explanation of why it is dose-related.

E. CARCINOGENICITY

1. Two Year Rat Study-

a. One year interim study-

Sponsor's statement of methods:

"A chronic toxicity study involving the administration of MJ 9022-1 and the positive control chlorpromazine HCl [CPZ] to rats was initiated at [redacted] Laboratories, [redacted] in June 1972. The present report contains the experimental procedure, and the results obtained from an interim 52 week sacrifice. The histopathological evaluation of the tissues obtained at this interim sacrifice was conducted by the Department of Pathology and Toxicology, [redacted]. These results are also contained in this report.

MJ 9022-1 was administered to rats mixed in the diet in concentrations designed to provide 0, 48, 80, or 160 mg/kg/day. Chlorpromazine HCl was employed as a positive control at a dietary level of 40 mg/kg/day.

Seventy males and 70 females were initially allotted to each of the treatment groups and 140 rats of each sex were placed in the control group. At the completion of 52 weeks 10 males and 10 females from each treatment group and 20 male and 20 female control rats were sacrificed for subsequent gross and microscopic examination.

All animals were individually weighed and food consumptions measured each week during the first 26 weeks and then every 2 weeks during the remainder of the 52 week period. Animals were observed daily for mortality. The incidence, time of appearance, location, size and change in character of palpable nodules or tissue masses in addition to pharmacotoxic signs were recorded. Hematology measurements consisting of hematocrit, hemoglobin concentration, RBC, WBC and differential counts were performed on 5 rats/sex/group at 13, 26, and 52 weeks. Serum chemistry measurements made at these same time intervals on 5 rats/sex/group include glucose, urea nitrogen, SGPT, alkaline phosphatase, total bilirubin, total protein, and protein electrophoresis, whereas serum Na, K, Cl, Ca, CO_2, SGOT, and total albumin were performed only at week 52. A urinalysis was performed using pooled urine samples from 5 rats/sex/group at 13, 26, and 52 weeks. Ophthalmologic examinations were performed using a binocular indirect ophthalmoscope once pretest and at week 52. As previously indicated 10-20 rats in all groups were sacrificed at 52 weeks and a complete gross pathologic examination was performed. Heart, liver, kidneys, spleen, and testes (with epididymides) were weighed at necropsy, while adrenals and thyroids were weighed after fixation. Body weights, food consumption and testicular weights (absolute and relative) were statistically analyzed by analysis of variance. A complete set of tissues was processed and examined histologically for the control and the 160 mg/kg/day dose group. Only target tissues were microscopically examined for animals receiving 48 and 80 mg/kg/day. All unusual lesions and tissue masses described at necropsy were histologically evaluated."

Results:

Mortality-

	Number Dead/total				
(Group Number)	1	2	3	4	5
	Control	48	80	160	CPZ
Males	4/140	3/70	2/70	2/70	4/70
Females	2/140	1/70	1/70	3/70	3/70

Observed Effects-

Number of hunched-appearing animals was increased in treated groups, especially HD groups after week 4. During weeks 10 and 11 mild tremors were seen in all buspirone-treated groups and beginning at week 12 and throughout the study, rapid respiration and tachycardia were seen. These effects were occassionally dose-related. MD and HD animals appeared hypersensitive and were seen digging in food jars resulting in food loss. Small testes were seen with increasing frequency from week 17, especially HD group, as was red or mucoid nasal discharge. Rough haircoat was seen primarily in chlorpromazine (CPZ) group. All other observations were thought to be spontaneous.

Growth/Food Consumption-

All buspirone treated groups and CPZ animals gained less weight and ate less food than controls. While the reduction in food consumption does not account for all the weight loss, the digging in food jars and subsequent loss of food may have biased the results.

Clinical Lab Studies-

No compound-related effects were seen in hematology. While occassional decreases in blood glucose were observed throughout treatment period there was no consistent effect. At 52 weeks, group mean values of the following were slightly below respective control values: sodium in HDM, potassium in MDM and HDM, Calcium in HDM and HDF, albumin in HDM, potassium in CPZ F.

There were no remarkable results from urinalysis.

Ophthalmic Exam-

No compound related effects.

Organ Weights-

Dose-related decreases in absolute weights for: thyroid in all males and females, heart in all males and HDF and CPZ F, liver and kidney in all animals, testes in HDM. There were no differences in relative organ weights.

Gross Necropsy-

Incidental findings only.

Microscopic Changes-

Dose-related increase in the number and incidence of foci of foamy macrophages in the lung sections were thought to be drug related. All other findings were considered incidental.

b. 2 Year Rat Study-

Methods:

The remaining rats from the one year interim study were continued on oral treatment of buspirone at 0, 48, 80 and 160 mg/kg/day in the diet. The following is the sponsor's explanation of the methods (both interim and 2-yr study):

"All animals were individually weighed and food consumptions measured every 4th week from week 53 through 104. Animals were observed daily for mortality. The incidence, time of appearance, location, size and change of character of palpable nodules or tissue masses in addition to pharmacotoxic signs were recorded. Hematology and serum chemistry parameters measured during the first 52 weeks of this study were repeated using 5 rats/sex/group at the end of this study (week 104). Urinalyses were performed using pooled urine samples from 5 rats/sex/group at the same intervals as the hematologic/serum chemistry measurements. Ophthalmologic examinations were repeated at week 104 using a binocular indirect ophthalmoscope. All surviving animals were sacrificed after 104 weeks of this study and a complete gross pathologic examination was performed. Similar examinations were performed on all animals which died or were sacrificed in a moribund condition during the study.

Heart, liver, kidneys, spleen and testes (with epididymides) were weighed at necropsy, while adrenals and thyroids were weighed after fixation. Body weights, food consumption and testicular weights (absolute and relative) were statistically analyzed by analysis of variance of F test. The incidences of neoplasms (both benign and malignant) were evaluated using the life-table analysis. The following tissues were processed and examined histologically for all rats: pituitary, thyroid, adrenal, lung, spleen, liver, kidney, testes, ovary, all unusual gross lesions and tissue masses. The remaining tissue types were examined histologically for 20 males and 20 females rats in the control groups and an equal number for both sexes in the group receiving 160 mg/kg/day of buspirone."

Results:

Observed effects-
The tremor, tachycardia and rapid respiration seen during first year were not significantly greater than control during the 2nd. Smaller testes were also not observed in surviving HDM. Red or mucoid nasal discharge was seen in a dose-related fashion throughout the study but was less apparent toward the end. Other observations were considered incidental.

Mortality-

Number Dead / Total
Percent of Total

Males					Females				
0	48	80	160	CPZ	0	48	80	160	CPZ
88/120	41/60	42/60	40/60	44/60	66/120	24/60	28/60	36/60	32/60
73%	48%	70%	67%	73%	55%	40%	47%	58%	53%

No differences between groups were seen.

Body weight/Food Consumption-
Dose-related decreased weight gain was seen throughout study and was significant at termination for all treated males and all but LD females. Food consumption data for the second year were not consistent and not directly related to growth. Again, spilling of food in MD and HD animals may have confounded the results. No statistical tests were performed.

Hematology-
At week 104 there were no group abnormalities or differences between groups, according to sponsor. However, tendencies included: dose-related increases in WBC in males and non dose-related increases in females.

Blood Chemistry-
At 104 weeks, low blood sugar levels were seen in 1 control male, 2 MDM and 1 HDM. High sugar levels were found in 1 LDM, and some females in the control, LD and MD groups; whereas HDF were normal. Slight to moderate elevated BUN was found in 6 males (2 control, 2 HD, 1 LD, 1 MD) and 1 control female. Mean SGPT values were slightly higher than control in HDM and CPZ M, whereas females means were normal. Mean ALK (alkaline phosphatase) values were

slightly higher for MDM and HDF. 1 HDM had very high ALK and SGOT. Mean SGOT tended to be slightly to moderately higher for all males and for HDF. Mean potassium values were slightly higher for all treated groups. Chloride values were below control for all MD and HD animals and CPZ F. Calcium was slightly lower in MD, HD, and CPZ males. Gamma globulin values were higher all MD and HD animals and in CPZ F.

Urinalysis-
No remarkable findings.

Ophthalmic Exams-
No compound related ocular changes.

Gross Pathology-
Changes occurring with greater frequency in treated groups at 104 week sacrifice include:

1) Liver with greenish or yellowish tinge in HDM.
2) Small spleen in HDM and CPZ F.
3) Dark renal medulla in LD and MDM.
4) Enlarged adrenals in LDF and MD and HD M and F.
5) Speckled or pale adrenals LDM and MDM.
6) Thickened stomach wall in LDF.

Of the animals which died during the study, there was found, in addition to the above changes:

1) Dark red or brown adrenals in males.
2) Thickened stomach wall in HDM and MDF.
3) Dark red stomach lining in MDM and HDM.
4) Ulcer-like lesion in stomachs of all males and females.

Organ Weights-
The following organ weights showed a slight to moderate dose-dependent decrease in absolute weight: thyroid- M and F; liver- M and HDF; spleen- F and HDM; kidney and testes- all groups. Of these, the following also showed relative weight decrease: thyroid- males; spleen- HDM; kidney- MDM, HDM. The adrenals showed a slight non-dose-related increase in absolute and relative weight in females and a larger, dose-related increase in males.

The only changes which are biologically significant, in my opinion, are:

1. Changes in spleen (primarily males)
2. Changes in kidneys and adrenals in males.

The gross pathology seems to be in accord with this.

Histopathology-

There were a greater number of deaths due to pituitary adenoma in LDM (5/29) and MDM (5/26) than in controls (6/59). HDM had no deaths for this adenoma (0/25). Non neoplastic lesions, and other changes, which occurred at a somewhat higher rate in treated groups include:

1) Brain: Focal encephalitis- control 0/45, HDM 3/23.
2) Lung: Foamy macrophages are dose-related and very numerous.
3) Stomach: Focal necrosis and gastritis in MDM and HDM.
4) Ovary: Greater number of corpus lutea in LD and MDF.
5) Thymus: Fat necrosis in 2/3 HDM.
6) Seminal vesicle atrophy: MD and HDM.

Tumor Incidence-

There were no statistically significant differences in tumor incidence between any groups. Non significant observations included: pheochromocytoma was seen more often in LDM (8/70) than in control (10/140). Malignant lymphoma was seen slightly more often in treated female groups: Control-(2/140), LD-(3/70), MD-(2/70), HD-(2/70).

Overall, there were no biologically relivant histological differences that would indicate specific drug toxicity which were not mentioned previously, i.e. foamy macrophages in lungs and inflammatory/necrotic lesions of G.I. tract.

2. Eighteen Month Mouse Study-

Sponsors statement of methods:

"The potential tumorigenic properties of buspirone were evaluated in a 78 week dietary study in the mouse. Groups of 66 male and 66 female CD-1 mice weighing 22-26 grams and 36-40 days of age were treated with diets (meal type) to provide 350, 700 and 1400 ppm, or approximately 50, 100 and 200 mg/kg/day, respectively of buspirone. An equal size group of both sexes received the basal diet and served as the control group. The animals were housed 3 per cage. Body weights and food consumptions were recorded weekly during the first 14 weeks and monthly thereafter. All animals were observed daily to detect deaths and significant changes in general condition. Animals were examined, including palpation for tissue masses, every 3 months during the first year and then once or twice a month until the end of the study.

Except during Weeks 67, 71, and 76, the groups were observed for motor function and subtle pharmacotoxic effects. Animals determined to be in a moribund condition, unlikely to survive, were sacrificed. A complete gross pathologic examination was performed on all animals found dead or sacrificed during or at the termination of this study. The adrenals, gonads, spleen, heart, brain, kidneys and liver from the first 10 surviving animals/sex/group were weighed at terminal necropsy, whereas the thyroids and pituitary were weighed after fixation in 10% buffered formalin. A complete set of tissues were processed and examined histologically for 20 male and 20 female surviving animals in the control group and the group receiving 200 mg/kg/day. The following tissues were processed and microscopically examined from all remaining mice: pituitary, adrenal, thyroid, lung, liver, gallbladder, spleen, kidney, gonads, all unusual lesions and tissue masses. Additional tissues were examined where necessary for animals dying during the study to determine the cause of death."

Results:

Mortality-
No differences between groups in number or cause of death.

Observed Effects-
Lacrimation, ataxia, inappropriate locomotion, decreased respiratory rate, obesity, alopecia and emaciation were observed during the study. The testing laboratory claims that there was no compound-related effects as these effects appeared in both control and treatment groups. This is highly unlikely and I will question the sponsor regarding it.

Body Weight-
Treated animals weighed less throughout study, especially males. There was very little if any difference between any of the treated groups, however.

Organ Weights-
Statistically significant changes occurred for the following organs:

Absolute increase in MDM heart and decrease in LDF and MDF hearts; absolute decrease in gonads of LDF and HDF; relative increase in heart of all males; relative decrease in gonads of LDF and HDF.

Gross Pathology-

Abnormalities were greater than controls for the following organs:

1) Lymph node enlargement in LDF.
2) Thymus enlarged in LDF and MDF.
3) Spleen enlarged or mottled in LDF, MDF and HDM.
4) Kidneys were pale in MDM.

Histopathology-

Amyloidosis occurred with greater frequency in the treated groups especially at the high dose. Tissues showing greater amyloidosis were:

Thyroid- MDM, HDM, HDF
Adrenal- all males and HDF
Salivary gland- HDM
Liver- HDM
Spleen- all males
Kidney- all males
Duodenum- HDM
Ileum- HDM
Testes- MDM, HDM
Ovary- LDF, HDF

Other changes possibly related to amyloidosis were:

Ovarian inactivity in HDF
Testicular atrophy in MDM and HDM
Pigmented kidney in all males
Pigmented liver in HDM
Thyroiditis in HDF

Neoplasms-

Buspirone treatment did not increase the type or incidence of adenomas or carcinomas of any type at any dose level. There was a trend toward a decreasing number of total neoplasms in males with increasing dose of buspirone. This is not an uncommon observation in such studies where treated animals may eat and weigh less than controls.

F. Special Studies

1. Drug Interactions -(submission page C3323)

Sponsor's Statement of Methods:

"The potential for buspirone to alter the sleep or paralysis times in the rat resulting from treatment with hexobarbital or zoxazolamine was determined using male Wistar rats approximately 4 weeks of age.

Groups of rats were treated with 5 daily doses of 18 or 36 mg/kg of buspirone given intraperitoneally, while the controls received 10 ml/kg of 0.9% saline. On Day 6, these pretreated groups were dosed intraperitoneally with either 120 mg/kg of hexobarbital sodium or 85 mg/kg of zoxazolamine and the time from the loss of the righting reflex until the rat spontaneously righted itself was measured. In separate groups given a single dose of 18 or 36 mg/kg of buspirone, the duration of sleep was established at 4 and 24 hours thereafter for hexobarbital or zoxazolamine."

Results:

The only significant effect was a slight increase of hexobarbital sleep 24 hr after a single dose of 36 mg/kg buspirone. The sponsor suggests this may be due to enzyme inhibition as repeated buspirone pretreatment eliminated this effect. However, there is no mention of why buspirone did not increase sleep when given 4 hr before hexobarbital. At this point in time, microsomal enzymes should be inhibited even more.

1. Ulcerogenic Potential.(C 3354)

Sponsor's Statement of Methods:

"Because of evidence of gastrointestinal irritation in monkeys dying during a 52 week study, which histologically was considered characteristic of spontaneous disease, a special study was conducted in the rat to quantify the potential of buspirone for gastrointestinal irritation. Groups of 5 male, CD rats weighing approximately 235-300 grams were dosed for 4 consecutive days under complete fasting conditions with either 0, 20, 40, 80 or 160 mg/kg/day of buspirone. All animals were sacrificed 24 hours after the final dose, the stomachs were removed, filled with saline and openings ligated prior to fixation in formalin for one hour. The stomachs were then opened along the greater curvature to permit grading of the mucosal surface for ulcerative changes."

Results:

Buspirone was significantly ulcerogenic at 80 and 160 mg/kg/day for 4 days, but not at 20 and 40 mg/kg/day.

IV. REPRODUCTION STUDIES

A. Segment I - Rat

The following is the sponsor's statement of the methods used in this study:

> "The potential effect of buspirone on the fertility and reproductive performance of the rat was assessed by mating treated female CD rats with non-treated males and vice versa. Groups of 30 virgin female rats (215-260 grams) were treated orally by gavage with either 9, 18 or 36 mg/kg/day of buspirone for 14 days prior to mating and continuing until 21 days postpartum. An additional group received 10 ml/kg of distilled water. A total of 15 females per group were sacrificed on day 13 of gestation and the uterine horns were examined upon removal for the distribution and the number of live or dead fetuses, empty implantation sites, and resorptions. The remaining dams were observed daily for difficulty in parturition. The pups were weighed and examined at birth for litter size, viability and possible gross abnormalities. Viability was determined again at day 4 after birth and at day 22 when pup body weights and final examination of each pup were performed.
>
> A second phase of the fertility and reproduction evaluation involved mating males and females both treated with buspirone and mating treated males with non-treated with buspirone at 9, 18 and 36 mg/kg/day in the diet for 63 days at which time the first 20 males per group were mated (1:1) with females treated for the 14 previous days via the diet at a similar dose level as her mate. The drug-diet was provided throughout the mating period. The last 10 males in each dose group were mated with 2 non-treated females per male. These males were treated during the mating period by gavage with suspensions of buspirone (in 0.5% methylcellulose) at a dose volume of 10 ml/kg. The pregnant animals were weighed weekly, examined for prolonged or difficult delivery, the number of dead and live offspring and the presence of pups; with gross abnormalities. Pup weights were recorded at birth and at weanling. The number and physical condition of all offspring were also recorded at days 4 and 22 of age."

Note: Duration of gestation was not measured.

Results:

1. Treated Females Only-

> The dams sacrificed at day 13 of gestation showed no treatment related effects on any parameter, i.e. number pregnant, number of fetuses, number of alive/dead fetuses.

Of the remaining rats treated until day 21 postpartum, there were no significant differences in the number becoming pregnant, having live litters, pups born alive, normal fetuses, or pup viability at 4 or 22 days. There were trends for fewer treated animals to become pregnant (control=93%, treated=73%), and a larger number of pups/litter in the treated groups which was significant for the LD group. Average birth weight was lower in the treated groups, partly because of a larger number of pups per litter. The average pup weight was significantly less at day 22 as were the number of pups surviving in the HD group.

2. Treated Males Only-
There were no treatment related effects on any of the parameters measured. There was one female pup born without a tail. This anomaly occurs spontaneously in this rat strain according to the sponsor.

3. Treated Males with Treated Females-
There were no differences in the number of: dams pregnant, littering or total pups. There were no effects on food consumption or weight gain in males or females during treatment. There were significant differences, however, in the litter weights. They were less at birth and at weaning in dams of the mid and high dose groups. Survival at 22 days was less for all treated groups: (HD- 91% surviving; Control- 98% surviving). These differences appeared to be due to maternal neglect resulting from pharmacological effects of buspirone.

Conclusion: There appear to be no fetotoxic effects or direct effects on reproduction with buspirone at doses approximately 40 times the maximum human dose. There was an effect on fetal survival, probably due to maternal toxicity which resulted in maternal neglect.

B. Segment II (Teratology)

1. Rat-

Sponsor's Statement of Methods:

"The potential teratogenic/embryotoxic properties of buspirone were evaluated in the CD rat. Four groups of 20 mature, virgin female rats weighing 260-300 grams were used in this study. On days 6-15 of pregnancy, groups were administered either 9, 18, or 36 mg/kg/day of buspirone. The control group received distilled water by gavage at 10 ml/kg. Body weights were determined on gestation days 0, 6, 13 and 20. On day 20 of gestation the females were sacrificed, the uterine contents removed and examined for the number of resorption sites (both early and late),

number of fetuses and location along the uterine horns (both dead and living), number of total implantation sites as well as empty implantation sites, fetal body weights, crown-rump distances and description of any pup with gross malformations. Approximately 50% of the fetuses from each litter were eviscerated and prepared for skeletal examination by a modified method of Green, while the remaining fetuses were fixed in 10% formalin and sectioned (free-hand technique of Wilson) to detect visceral anomalies."

Results:

There were no differences or trends for differences between control and buspirone-treated groups. The only anomalies were 2 pups with apparent hydrocephaly, 1 in the control and 1 in the LD group.

2. Rabbit-

Sponsor's Statement of Methods:

"A teratogenic evaluation was conducted in the adult Dutch-Belted rabbit. Groups of 15 rabbits weighing approximately 1.75-2.55 kg were artificially inseminated after inducing ovulation with an injection of pituitary luteinizing hormone. These groups were treated by gavage on days 6-18 of gestation with 9, 18 or 36 mg/kg/day of buspirone. The control group received 1.0 ml/kg of distilled water. All does were weighed on day 0, 6, 16, 23 and 29 of gestation. After sacrifice on day 29 of gestation, the uterine contents were removed and examined for the number of resorption sites (both early and late), number of fetuses and location along the uterine horns (both dead and living), number of total implantation sites as well as empty implantation sites, fetal body weights, crown-rump distances, gross pup malformations and viability during incubation for 24 hours after the examination. After the incubation period all fetuses were euthanized. Approximately 50% of the fetuses from each litter were skinned, eviscerated and prepared for skeletal examination by a modified method of Green, while the remaining fetuses were fixed in solution and sectioned (free-hand technique of detect visceral anomalies."

Results:

General-There was a slight weight loss among animals of the MD group. One death occurred in the control and 3 in the HD group. The cause of death was undetermined in the treated group but fetuses appeared to be developing normally. The control animal had aborted 3 fetuses when found dead.

There were no differences between groups for the following parameters: number of implantation sites, dead fetuses, number of resorption sites, mean crown-rump distance, gross anomalies (none in any group), live fetuses at 6 or 24 hr.

There were differences between groups for the following parameters: Number of empty implantation sites were greater among controls (9) than treated (3 in LD and 0 in MD and HD). The litter size was greater for LD group (mean = 6.3) than control (mean = 4.8) MD (mean = 9.3) or HD (mean = 5.6). The mean fetus weight was thus lower in the LD group, and was unexpectedly high in the HD group (control=38, LD=31, MD=36, HD=49 g).

Skeletal anomalies encountered were 2/30 in the MD group from the same litter (1 had fused 4th and 5th sternebra and 1 had disarranged sternebra) and 1/30 in the HD group (2nd sternebra fragmented in 2 pieces). There were no visceral anomalies in any group.

Conclusion: Buspirone does not appear to be teratogenic or fetotoxic at doses up to 36 mg/kg/day (approximately 40 times the maximum recommended human dose).

C. Segment III - Rat

Sponsor's Statement of Methods:

"The potential effect of buspirone on fetal development was assessed in a peri-postnatal study using adult CD Rats. Groups of 20 female rats were treated by gavage with either 9, 18 or 36 mg/kg/day of buspirone beginning on day 15 of gestation and continuing through day 21 postpartum. The control group received 10 ml/kg of distilled water. The dams were weighed weekly and examined daily especially during the times of expected parturition to detect delayed or prolonged delivery and to prevent cannibalism of weak or dead fetuses. Upon delivery, all pups were carefully examined for size, sex, and gross abnormalities. The number of living or dead fetuses was recorded. Body weights were recorded at birth and at 21 days of age. The number of pups was recorded at birth, days 4 and 21 of age. The littering, fertility, survival and lactation indices were determined for each litter."

Results:

There were no maternal mortalities during the study. All pregnant rats bore live pups except one control. All parameters measured were comparable between control and busprione-treated groups. The CPZ-treated group had a slightly lower fertility

index (89%) and the survival index was considerably lower (43%). This appeared to be due to neglect during the immediate post-partum period. Gestation length was also longer (22.3 days compared to 21.6 days).

Non-significant trends were as follows:

	Buspirone 0 (Control)	B 9	B 18	B 36	CPZ 36
Pups born alive	209	226	232	204	179
Pups born dead	2	0	4	17	17
Average birth wt(g)	6.5	6.5	6.2	6.0	5.6
Alive at 4 days	208	224	228	193	79
Alive at 21 days	204	223	216	188	77

Conclusion: There is no significant effect from buspirone treatment on peri and postnatal development at doses up to 36 mg/kg.

D. Mutagenicity

1.

Sponsor's Statement of Methods:

"The potential for buspirone to increase the histidine reversions of 5 auxotrophic strains of Salmonella typhimurium in the presence or absence of metabolic activation was assessed at 5 different concentrations (185; 555; 1,667; 5,000; and 15,000 mcg/plate). A preliminary study was performed using the TA100 strain to establish the toxicity of buspirone to the bacterial cell, based on survival and to provide data for selection of the test concentrations. Buspirone, dissolved in deionized water, was added to a test tube containing agar, the tester strain and if indicated the S-9 fraction from rat liver homogenate for metabolic activation. The contents were mixed, poured onto agar plates, rotated and tilted for uniform distribution and incubated after hardening. Revertant colonies for buspirone and the positive controls (methylnitronitrosoguanidine, 9-aminoacridine, 2-nitrofluorene and 2-aminoanthracene) were counted with an electronic colony counter."

Results:

No appreciable increase in reversion to histidine prototrophy resulted from nontoxic doses of buspirone, nor did metabolic activation change these findings.

2. Mouse Lymphoma Mutagenesis Assay

Methods:

Microbiological Associates tested buspirone in the L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay in the presence and absence of Aroclor induced rat liver S-9. The nonactivated cultures were cloned at concentrations of buspirone which produced 50 to 98% total growth, while S-9 activated cultures were cloned with concentrations of buspirone which produced 99 to 134% total growth. In additional studies, other concentrations of buspirone were used which produced various percentages of total growth due to erratic dose-response toxicity.

Results:

None of the cultures that were cloned showed mutant frequencies which were significantly different from the mean mutant frequency of the solvent controls, either in the presence or absence of exogenous metabolic activation.

Thus, in this assay, buspirone was free from mutagenic activity at concentrations up to 1001 mcg/ml.

3. Unscheduled DNA Synthesis

Sponsor's Statement of Methods:

"The in vitro DNA repair assay, using a WI-38 human cell line, was performed to evaluate the genotoxic potential of MJ 9022-1 (Buspirone HCl) containing 91.4% base. WI-38 cultures were incubated at 37°C with 5% CO_2 in a humidified atmosphere and used at passage #21. Complete culture medium consisted of 90% Minimal Essential Medium (MEM), 10% fetal calf serum, non-essential amino acids and antibiotics. After the final subculture, the cell line was examined for the presence of mycoplasma and exhibited no contamination.

The DNA repair assay was conducted in the presence and absence of mixed-function oxidase (MFO) metabolic activation. The S-9 fraction of liver homogenate was obtained from male rats that were stessed with a single intraperitoneal (IP) injection of Aroclor 1254 in corn oil.

At cell confluency, test article cultures were treated with MJ 9022-1 at final concentrations of 274.2, 137.1, 68.6 and 34.3 mcg/ml (in terms of MJ 9022-1 base). Similar sets of cultures were exposed to the positive control articles 4-nitro-quinoline- N-oxide (4-NQO) and aflatoxin B_1 (AFB_1). The negative control, 0.9% dimethylsulfoxide (DMSO) in MEM, also served as a vehicle for the test article.

After approximately 4 hours of chemical exposure, the cells were rinsed with phosphate buffer containing 0.1% thymidine and fixed *in situ* with 1:3 glacial acetic acid-ethanol. Microslides, cut from culture flasks, were coated with Kodak NTB-2 liquid emulsion, maintained at 0-4°C for 6 days and processed with Kodak D-19 developer and Kodak fixer. Slides were then stained with ___ R-66 Giemsa.

Nuclei were examined for the presence of silver grains indicating unscheduled DNA synthesis (UDS), a repair mechanism for DNA damaged by chemical insult to the cells."

Results:

Both 4-NQO and AFB_1 caused an increase of UDS compared with the negative control. However, no UDS was seen at any concentration of buspirone in either metabolically activated or non-activated systems.

4. In Vivo Cytogenetics in Mice

Sponsor's statement of methods:

"An *in vivo* cytogenetic assay, using male mice of approximately 9 weeks of age and weighing between 27 and 40 grams, was performed to evaluate the potential of MJ 9022-1 to induce chromosomal aberrations. Mice were given either single or multiple IP injections of MJ 9022-1 at dosage levels of 18.3, 6.4 and 1.8 mg/kg (in terms of MJ 9022-1 base). Multiple injections (acute sequence) consisted of 5 doses, approximately 24 hours apart. Triethylene melamine (TEM) was used as the positive control article. Both TEM and MJ 9022-1 were prepared with Travenol water which was also used as the negative control.

After treatment, all animals were observed daily for viability and the acute sequence dose volumes were readjusted according to changes in daily body weights.

Approximately 3.5 hours prior to termination, mice were injected IP with colchicine at a dose of 4.0 mg/kg. Animals of the single dose sequence were sacrificed approximately 6, 24 and 48 hours after dosing. Multiple-dosed mice were sacrificed on the fifth day of injection, approximately 6 hours after the last dose. After termination, marrow was removed from both femurs and metaphase spreads were prepared. Slides were then stained with* R-66 Giemsa."

Results:

Of fifty metaphases examined from each animal having scorable metaphase cells, no significant increase of aberrations or other abnormalities were apparent with any dose level of buspirone. TEM, however, was extremely elastogenic at 1 mg/kg.

Conclusions:

The results of the above assays suggest that buspirone is non-genotoxic at concentrations of up to 274 ug/ml in cell culture or 18.3 mg/kg/day for 5 days, in vivo.

PACKAGE INSERT:

1. The statement in the second paragraph of page 2, concerning buspirone's effects on dopamine systems is, at best, an incomplete characterization of complex data from several sources. It states:

   "Animal studies have shown buspirone to markedly activate certain dopaminergic pathways in the brain via blockade of both dopaminergic and GABAergic inhibition."

   One might conclude fron this statement that buspirone enhances the functional activity of dopamine (DA) neuronal systems. I feel it would better define buspirone's activity in terms of how it actually affects DA mediated behaviors, neurochemistry and electrophysiology. For example, buspirone may act in a manner characteristic of a neuroleptic, a DA agonist, or in other ways which are unique to buspirone (see tables, pages 54, 55 and 56).

2. Dose ratios which make comparisons between those used in animal toxicity studies (i.e. carginigenesis, mutagenesis, impairment of fertility) and human doses, should use the maximum recommended human dose (60 mg/day) which would be equal to 1.2 mg/kg/day for a 50 kg adult.

3. LD_{50} values given for animals on page 11 should reflect male and female of the species. The LD_{50}s given for mice and rats refer only to males.

A final point is in regard to buspirone metabolites. The 1-pyrimidinylpiperazine (1-PP) metabolite mentioned on page 3 of the Package Insert is insufficiently characterized. ' group in nave reported that 1-PP is present in considerably higher concentrations than the parent compound in rats. In addition, brain concentrations of both buspirone and 1-PP were higher than in plasma and the half-life of 1-PP was 4 to 5 times that of buspirone. Since 1-PP and possibly other metabolites are active, they should be further characterized, both clinically and preclinically.

SUMMARY AND EVALUATION:

Buspirone is an anxiolytic with a unique, non-benzodiazepine structure. It has a behavioral profile in preclinical tests which are predictive of anxiolytic activity, yet it has neither anticonvulsant nor muscle relaxant properties. Buspirone also lacks sedative-hypnotic activity within the anxiolytic dose range. It is therefore a unique agent when compared with marketed anxiolytics.

Buspirone is a water soluble, easily absorbable compound supplied in 5 mg and 10 mg scored, white tablets. The recommended dose range is 20 to 30 mg/day with a maximum of 60 mg/day. It is indicated for the management of anxiety disorders or the short-term relief of symptoms of anxiety, with or without accompanying depression.

Buspirone is also active in behavioral tests predictive of antipsychotic, or neuroleptic, activity. However, the doses used in these studies were generally higher and/or administered parentarally. Anxiolytic activity is more prominent after oral administration and is seen at non-sedative doses (1 to 5 mg/kg).

The precise mechanism of action of buspirone has yet to be defined. It does not bind to benzodiazepine or GABA receptor sites, either in vitro or in vivo. The only brain receptor for which buspirone has been found to have significant affinity is the DA receptor. This finding is consistent with the weak neuroleptic activity of buspirone in animal behavioral models.

The interaction with DA receptors, however, is complex and not yet fully characterized. Under some conditions, buspirone acts like a DA antagonist and in others like a DA agonist. The behavioral effect appears to be somewhat dependent on the state of the organism prior to treatement. For example, buspirone is capable of antagonizing both the stereotypy induced by apomorphine and the catalepsy induced by neuroleptics.

EVIDENCE FOR DOPAMINE (DA) ANTAGONIST EFFECTS

Evidence for DA Antagonism	Buspirone ED_{50} (mg/kg)
1. Inhibition of conditioned avoidance response (CAR)	
rat:	3.6 - 4.3 i.p.
mouse:	10 - 48 p.o.
	37 i.p.
monkey:	71 p.o.
	2 - 16 i.m.
2. Inhibition of apomorphine-induced behaviors	
hypermotility in mice:	32 i.p.
stereotypy in rats:	28 p.o.
emesis in dogs:	5 i.v.
3. Inhibition of ^3H-spiperone binding in vitro	IC_{50} = 260 nM
4. Increase in DA neuronal activity (turnover) in vivo	
Increased accumulation of HVA and DOPAC	2.5 - 50 p.o.
	0.03 - 10 s.c.
	1.0 - 3[illegible] i.p.
Increased accumulation of DOPA after decarboxylase inhibition	10 i.p.
5. Increase in prolactin release in vivo	0.5 - 50 i.p.
in vitro	1 uM
6. Increase in DA neuronal firing rate and blockade of DA-induced decrease	5 - 320ug/kg i.v.
7. Enhanced depletion of DA after alphamethyltyrosine	5 and 25 i.p.
8. Antipsychotic effects in humans?	Mega

EVIDENCE FOR DA AGONIST ACTIVITY

BUSPIRONE EFFECT	DOSE (mg/kg)
1. Reverses catalepsy induced by trifluoperazine by haloperidol, cis-flupenthixol, and Ro 4-1284	3.6 p.o. 1.0 s.c.
2. Reduces striatal DOPA formation in GBL-treated rats	7.0 p.o.
3. Induces contralateral turning in unilateral substancia nigra-lesioned rats	1.25 - 2.5 s.c.
4. GTP reduces buspirone displacement of ^{3}H-spiperone binding as it does DA agonists	from 273+31 nM to 381+68 nM
5. EEG profile in rabbits, cats and rats is similar to agonists and dissimilar to antagonists	0.5 i.v. or s.c.
6. Antagonises electrically-induced enhancement of perfusion pressure in isolated rabbit ear artery	30 uM
7. Decreases renal resistance and increases GFR in dogs	167 ug/kg/min i.v.

OTHER RELEVANT EFFECTS OF BUSPIRONE ON DA SYSTEMS

EFFECT	Dose (mg/kg)
1. Increases DA neuronal firing beyond the increase induced by haloperidol (implying a different mechanism)	0.1 - 1.0 i.v.
2. Displacement of DA and apomorphine binding is incomplete at 1.0 mM (25 and 47%, respectively) while displacement of N-n-propylnorapomorphine is complete	1.0 uM
3. Antagonises decreased DA neuronal firing induced by both DA and GABA iontophoretic application	iontophoretic
4. Fails to block apomorphine-induced contralateral turning in SN-lesioned rats	3.0 s.c.
5. Does not induce catalepsy in rats	200 p.o. 32 i.p.
6. Does not increase neuronal concentrations of 3-methoxytyramine(3-MT) at doses which increase HVA and DOPAC	2.5 - 50 p.o.
7. Weak antagonism of DA-stimulated adenylcyclase	100 uM
8. Does not increase striatal spiperone binding after chronic treatment as do neuroleptics	study - 2.0 p.o.,tid/29 days study - 20 p.o.,bid/25 days study - 6 i.p./day/30 days
9. Buspirone and molindone cause selective enhancement of DA metabolism in striatum and not in cortex (unique effect)	0.03 - 3.0 s.c.

The sponsor proposes that the anxiolytic activity of buspirone is somehow related to it's effects on the DA system. I seriously doubt this conclusion. Although the sponsor has not sufficiently addressed this alternative, there is considerable evidence that the anxiolytic activity of buspirone is due to a metabolite(s) such as 1-pyrimidinylpiperazine (1-PP), while the DA activity is due solely to the parent compound. This is evidenced by the following points:

1. Early preclinical studies in rats reported that doses of buspirone (1-5 mg/kg) which were inactive in conflict procedures when given i.p., were active when given orally.

2. Anxiolytic activity in monkeys was apparent the day after a single i.m. dose and persisted for up to 2 weeks (the half life of the parent compound is only a few hours).

3. Antidopaminergic properties of buspirone, as determined by preclinical, neurochemical and behavioral models, as well as antipsychotic properties in humans, are of very short duration compared with the anxiolytic properties.

4. Receptor binding studies indicate that only buspirone, itself, interacts with DA receptors. The 1-PP metabolite, which has been shown to have anti-conflict activity in animals, does not have affinity for the DA receptor, nor does it possess neuroleptic properties.

5. Oral administration of 10 mg/kg buspirone to rats fails to produce measurable plasma levels of buspirone (less than 1 nM/ml) while the 1-PP metabolite shows an AUC and Cmax (8.5 nM/ml) similar to that found after 10 mg/kg i.v. buspirone or 1-PP.

Toxicity studies performed with buspirone include:

ACUTE TOXICITY

Species	Sex	Route	LD_{50}(mg/kg)
Rat	M	p.o.	265
Rat	M/F	p.o.	196
Rat	M/F	i p.	136
Mouse	M	p.o.	665
Mouse	M	i.p.	164
Mouse	M	i.v.	73
Dog	M/F	p.o.	586
Dog	F	i.v.	125
Monkey	M/F	p.o.	356
Monkey	M/F	i.v.	54

In all species, death was preceded by clonic convulsions and profuse salivation.

SUBACUTE TOXICITY STUDIES

Species	Duration	Doses (mg/kg,p.o.)			
Rat	3 Month	0	50	100	200
Rat	1 Year	0	48	80	160
Rat	2 Year	0	48	80	160
Mouse	18 Month	0	50	100	200
Monkey	3 Month	0	37.5	75	150
Monkey	1 Year	0	35	62	110
	reduced to	0	25	31X2	55X2
	reduced to	0	25	25X2	50X2

In rodents, buspirone was given by mixing with the food. This may be partly responsible for a dose-related decrease in weight gain seen in both rats and mice. In the 1 year rat study, other signs of dose-related toxicity included the appearence of foamy macrophages in the lung, rapid respiration and tachycardia. In the 2 year rat study, there were numerous pathological changes including organ weight increases (adrenals) and decreases (spleen and kidneys in males), and minor blood chemistry changes. None of these effects appeared to be deleterious to the animals or affect their survival.

There were also treatment related gross and histopathological changes (primarily amyloid deposition in various tissues) in the 18 month mouse study which did not affect survival.

Buspirone did not increase the frequency or type of tumors in either species.

In the monkey, there were behavioral effects which were clearly toxic and dose-related from 25 mg/kg b.i.d. and above (by oral gavage). Behaviors such as tremor, salivation, hypoactivity and anorexia could be seen at the lowest dose (25 mg/kg) and intensified with increasing doses. Catatonia and repetitive chewing on the wrists and cage were seen at the higher doses. Hematology changes similar to those in the rat (i.e. decrease in RBC and PCV) were seen in both LD and HD animals. Organ weight changes occurred for several organs beginning at the LD, and were generally dose related. No histopathology changes were noted.

Note: In a pharmacokinetic study, monkeys could not tolerate single doses of 25 mg/kg/day p.o. One female died after the first dose and the other had clonic convulsions on day 3. While one male completed the one week course with only hypoactivity, while other had seizures on day 4. This paradox was not addressed by the sponsor.

A true no effect dose cannot be chosen for any species tested, and increased mortality was seen in all species but mice.

REPRODUCTION STUDIES

Segment I -
Rats: Females were treated with 9, 18, and 36 mg/kg/day in the diet 14 days prior to mating until 21 days postpartum. Males were treated 63 days prior to mating and during mating period.

Segment II - (Teratology)
Rats: Treated day 6 - 15 of gestation with 9, 18, and 36 mg/kg/day buspirone.
Rabbits: Treated day 6 - 18 of gestation with 9, 18, and 36 mg/kg/day buspirone.

Segment III -
Rats: Treated day 15 of gestation to day 21 postpartum with 9, 18, and 36 mg/kg/day buspirone.

Throughout these studies there was no direct fetotoxicity observed. In the Segment I study, the pups of the treated females weighed slightly less than the controls, and pup survival at day 22 was less. However, this was most likely due to maternal neglect resulting from the high dose of buspirone. There was was a non-significant increase in the number of dead fetuses in the Segment III study for the same reason. No significant toxicity or teratogenic effects were seen in the Segment II studies.

No evidence for mutagenicity was found for buspirone in the Ames test, the mouse lymphoma mutagenesis assay, the unscheduled DNA synthesis test or the in vivo cytogenetics test in mice.

I consider these studies to be an adequate evaluation of buspirone's toxicity and is sufficient for NDA approval. The only deficiency I see is the failure of the sponsor to deal with the 1-PP metabolite of buspirone, as described previously. I do not consider this shortcoming to be grounds for non-approval, however.

RECOMMENDATIONS:

I recommend that this NDA be approved. I see no grounds for refusal to approve the application based on the adequacy or scope of testing or on the labeling.

Jerry M. Cott

Jerry M Cott, Ph.D.

cc:
Orig. NDA 18-731
HFN 220
HFN 120
HFN 120/JCott/7/27/83
HFN 102/Glockiin
RD/init:JContrera
rd/AAK/6/7/83/8/15/83/9/17/83/9/19/83
Doc. 6474B

CHEM REVIEW

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA/BD # 18-731

Applicant: Mead Johnson
Sponsor: Evansville, Indiana 47721
Address:

Division: DNDP (HFD-120)
Chemist Review # 1
Reviewing Chemist: F. A. Zinsitz

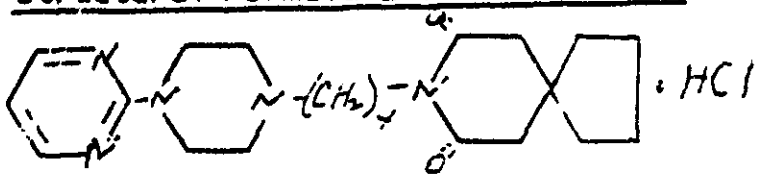
Date Completed: March 9, 1983

Product Name(s):
Proprietary: Buspar
Non-proprietary: buspirone hydrochloride
Compendium:
USAN: buspirone hydrochloride
Code name/number: MJ 9022-1

Dosage Form(s) and Route(s) of Administration: Tablets, oral

Pharmacological Category and/or Principal Indication: Anxiolytic

Structural Formula & Chemical Name:



8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione hydrochloride

Initial Submission: December 15, 1982 (Rec'd. in BD 12/15/83 and for Rev. 1/4/83)
Amendment(s): February 4, 1982 (Rec'd for Rev. 2/8/83)
Related Documents:

Remarks: The deficiencies noted in the attached review may be briefly summarized as follows: 1) Letters of authorization are needed from each of the suppliers of packaging components; 2) Updating of the referenced DMF is needed to be in agreement with the specifications and tests included in the NDA; 3) The limited stability data only supports a 2 year expiration dating; 4) Clarification and complete supporting documentation is needed for "rework" procedures alluded to on pages B 714 and B 720; 5) Container labels are needed for the unit dose flexible and sample packages.

Conclusions and Recommendations:

Non-approvable. However, the comments under Remarks, above, may be communicated to the applicant by the reviewing chemist on concurance with the Supervisory Chemist.

3/9/83
Francis A. Zinsitz 3/9/83
Chemist

cc: HFD/NDA Orig.
HFD-102/Kumkumian (Only Chemist's Review # 1's)
HFD-120
HFD-120/FZinsitz 3/9/83

NDA/[redacted] = 18-731

Applicant: Mead Johnson
Sponsor: Evansville, Indiana 47721
Address:

Div: D: DNDP (HFD-120)
Chemist Review = 3
Reviewing Chemist: F. A. Zinsitz

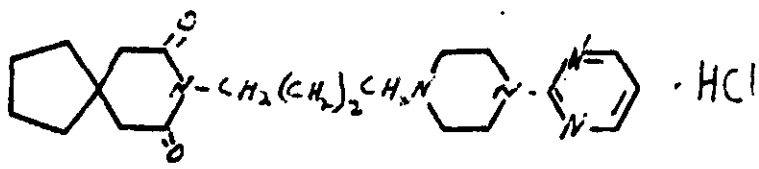
Date Completed:

Product Name(s):
Proprietary: Buspar
Non-proprietary: buspirone hydrochloride
Compendium:
USAN: buspirone hydrochloride
Code name/number: MJ 9022-1
Drug Classification: 1 B

Dosage Form(s) and Route(s) of Administration: Tablets, oral

Pharmacological Category and/or Principal Indication: Anxiolytic

Structural Formula & Chemical Name:



8-[4-[4-(2-pyrimidinyl)-1-piperainyl]butyl]-8-azaspiro[4,5]decane-7,9-dione hydrochloride

Initial Submission: December 15, 1982
Amendment(s): 2/4/82; 10/6/83; 11/11/83; 12/2/83; 6/13/83; 5/16/83
Related Documents:

Remarks: The applicant's submission dated June 13, 1983 is a partial response to telephone conversations with Dr. J. Cott of this agency regarding pharmacology report deficiencies. The applicant's submission dated October 6, 1983 is in response to a telephone conversation with Mr. Zinsitz of this agency on August 12, 1983 which states that the applicant withdraws reference to use of unit-dose packaging and agrees to revise the container label recommended storage to read "Store at temperatures not to exceed 86°F (30°C). Dispense in a tight, light-resistant container (USP)." using a larger size type. The applicant has provided additional comparative HPLC high sensitivity tracings obtained from old and modified synthesis to demonstrate that the impurities present in the drug product remain within specifications.

Conclusions and Recommendations:

The application is approvable with regard to manufacturing and controls.

Francis A. Zinsitz 1/18/84

Francis A. Zinsitz 1/18/84
Chemist

cc: ~~XXX~~NDA Original 18-731
HFD-120/Kumkumian (only Chemist's Review #1)
HFD-Division File DET-DO, HFN 120, HFN 120/FZinsitz/1/18/84, RD/init:RShultz/1/18/84
HFD-[illegible]/drafter/date/typist/date

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

AUG 22 1986

NDA # 18-731

Applicant: Bristol-Myers Co.
Address: Wallingford, CT. 06492

Division:	HFN-120
Chemist Review:	#4
Reviewing Chemist:	F. A. Zinsitz
Date Received:	8/8/86
Date Completed:	9/19/86
Received CDB:	8/5/86

Product Name:

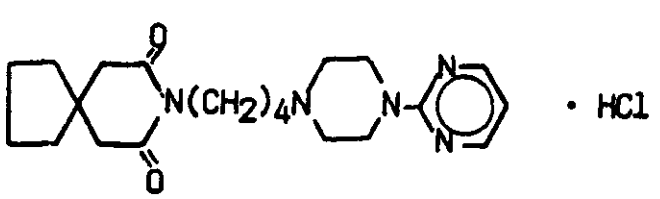
Proprietary:	Buspar
Non-Proprietary:	buspirone hydrochloride
USAN:	buspirone hydrochloride
Code Name/Number:	MJ 9022-1
Drug Classification:	1B

Dosage Form(s) and Route(s) of Administration: Tablets, oral.

Pharmacological Category and/or Principal Indication: Anxiolytic

Structural Formula & Chemical Name:

N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride



Initial Submission: December 15, 1982

Amendments: See Chem. Rev. #3 dated 1/18/84 for prior listing. August 5, 1986.

Related Documents: See Chem. Rev. #3 dated 1/18/84.

Remarks:

Amendment dated 8/5/86 is in response to FDA approvable letter dated 7/17/86. The DESCRIPTION section of the package insert now provides for listing the inactive ingredients of the tablets; however, the mixed order of listing is not consistant with the agreement stated in FDA letter dated 1/28/85 signed by Dr. Harry Meyer, Jr. in response to the PMA Guideline dated 12/5/84 which requires that the inactive ingredients be listed in alphabetical order. The HOW SUPPLIED section of the package insert includes acceptable revised information as required by 21 CFR 201.57(k).

Conclusions and Recommendations:

Although the application remains approvable for Chemistry, the applicant should revise the DESCRIPTION section of the package insert as noted above.

Francis A. Zinsitz 8/19/86
Francis A. Zinsitz (8/19/86)

cc: ORIG:IND or NDA
HFN-120/F. A. Zinsitz(8/19/86)
INIT:RCShultz/
DOC# 2205D

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

SEP 15 1986

NDA # 18-731

Applicant: Bristol-Myers Co.
Address: Wallingford, CT. 06492

Division:	HFN-120
Chemist Review:	#5
Reviewing Chemist:	F. A. Zinsitz
Date Received:	9/9/86
Date Completed:	9/11/86
Received CDB:	9/3/86

Product Name:

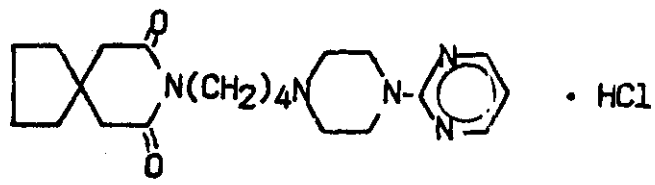
Proprietary:	Buspar
Non-Proprietary:	buspirone hydrochloride
USAN:	buspirone hydrochloride
Code Name/Number:	MJ 9022-1
Drug Classification:	1B

Dosage Form(s) and Route(s) of Administration: Tablets, oral.

Pharmacological Category and/or Principal Indication: Anxiolytic

Structural Formula & Chemical Name:

N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride



Initial Submission: December 15, 1982

Amendments: See Chem. Rev. #4 dated 8/19/86 for prior listing. Sept. 2, 1986.

Related Documents: See Chem. Rev. #3 dated 1/18/84.

Remarks:

Amendment dated 9/2/86 is in response to FDA approvable letter dated 7/17/86 and meeting at agency on Aug. 29, 1986. The DESCRIPTION section of the package insert now provides for listing the inactive ingredients of the tablets in alphabetical order. The HOW SUPPLIED section of the package insert includes acceptable revised information as required by 21 CFR 201.57(k).

Conclusions and Recommendations:

The application remains approvable with regard to Chemistry.

Francis A. Zinsitz 9/11/86
Francis A. Zinsitz (9/11/86)

cc: ORIG:IND or NDA
HFN-120
HFN-120/F. A. Zinsitz(9/11/86)
INIT:RCShultz/
ft/FAZ/9/11/86
DOC# 2371D

ANALYTICAL METHODOLOGY

BUSFAR

METHODS

Color: Examine the sample macroscopically, visually observing the color of the sample.

Identification;

A. Infrared Spectrum: Record the infrared spectrum of a KBr dispersion (2 mg/300 mg) and compare the spectrum to that of the KBr dispersion of the reference standard.

B. TLC:

Equipment and Reagents

Plate: Silica Gel 60 F254, 250 microns, glass .

Developing Solvent: Chloroform/absolute ethanol (88/12).

Standard Solution: 10 mg. of reference standard dissolved in 1 ml. of chloroform.

Sample Solution: 10 mg of sample dissolved in 1 ml of chloroform.

Procedure

Line the sides of the chromatography chamber with filter paper. Completely wet the filter paper with the developing solvent by pouring down the sides of the chamber. Fill the chamber to a depth of about 0.5 cm with the developing solvent. Tightly seal the chamber and allow to equilibrate for 20 minutes.

Activate the silica gel 60 plate in a 105° oven for 20 minutes. Cool the plate at room temperature for 5 minutes and place in a desiccator until ready to spot. Spot 10 µl of sample and standard at least 2 cm from the bottom edge of the plate and keep the spots 1.5 to 2 cm apart.

Place the bottom end of the plate into the solvent in the chamber resting the upper end against the side of the chamber. Seal the chamber and allow the solvent to move up the plate to about 10 cm from the origin. Remove the plate and allow to air dry.

Expose the sheet to ultraviolet light and note any spots that may be present. (These should be outlined in pencil while viewing under the UV light.)

Solubility:

A. Water: Dissolve 0.5 g of sample in 25 ml of distilled water and visually examine the resulting solution.

B. Ethanol: Dissolve 0.5 g of sample in 25 ml of ethanol and visually examine the resulting solution.

C. Chloroform: Dissolve 0.5 g. of sample in 25 ml of chloroform and visually examine the resulting solution.

Melting Range: Determine in accordance with the USP <741>, Class Ia.

Moisture: Determine in accordance with the USP <921>, Method I (Titrimetric Method).

Residue on Ignition: Determine in accordance with the USP, <281>.

Heavy Metals: Determine in accordance with the USP, <231>, Method II.

Chloride: Transfer about 400 mg of accurately weighed sample to a 250 ml beaker. Dissolve the sample in 20 ml. of water and add 3 ml of concentrated nitric acid. Pipet 20.0 ml of 0.1 N silver nitrate VS into the beaker. Gently boil the mixture for about 5 minutes

Place a Whatman No. 50 filter paper in a Buchner funnel and wet the paper. Filter the sample, using moderate vacuum to avoid foaming, and rinse the boiling flask and funnel with a total of 80 ml of water in several portions. Add 2 ml of ferric ammonium sulfate TS and stir rapidly while titrating from a 25 ml buret with 0.1N ammonium thiocyanate VS to the faint red-brown endpoint.

$$\% \text{ chloride, w/w} = (\text{ml } AgNO_3 \times \underline{N} - \text{ml } NH_4SCN \times \underline{N}) \times \frac{35.45}{\text{wt sample (mg)}} \times 100$$

Residual Solvents;

A. Individual:

Solutions

1. Standard Solution - Pipet 1.40 ml (1000 mg) of anhydrous ether and 1.25 ml (1000 mg) of isopropanol into a 100 ml volumetric flask. Dilute to volume with N,N-dimethyl-acetomide and mix well. Pipet 1.0 ml of this solution into a second 100 ml volumetric flask, dilute to volume with

N,N-dimethylacetamide and mix well (0.1mg/ml).

2. Sample Solution - Transfer about 100 mg of sample, accurately weighed, to a 10 ml volumetric flask. Dissolve in and dilute to volume with N,N-dimethylacetamide.

Chromatography Guidelines

Systems and conditions giving comparable results may be used.

Instrument:	Any instrument capable of accepting the column, equipped with an FID and operating under the outlined conditions is acceptable.
Column:	6'x4 mm ID glass containing 28% Pennwalt 223/4% KOH on 80/100 mesh Gas Chrom R.
Column Temp:	100° initial. Six minutes after the injection, the temperature is raised to 180° at 8°/min and held at 180° for five minutes or until all peaks have eluted.
Carrier Gas:	Helium at 50 ml/min.
Injector Temp:	200°C.
Detector Temp:	300°C.
Chart Speed:	0.5 cm/min.
Typical Retention Times:	Ether 1.73 min. IPA 2.94 min. DMAC 16.62 min.

Procedure

Chromatograph duplicate microliter aliquots of the standard and sample solutions after the guideline parameters have been optimized. Duplicate standard solution injections should be made after every fourth injection series of sample solution and at the end of the run.

Calculations

$$\% \text{ Residual Solvent, w/w} = \frac{A}{B} \times \frac{D}{C} \times E \times 100$$

A = average area of sample peak
B = average area of standard peak
C = sample weight, mg
D = standard weight, mg = 1000 for both ether and IPA
E = dilution factor = 0.001

B. Total

Add the results for isopropanol and ether. Report the total.

Chlorobuspirone:

Standard Preparation

Transfer about 10 mg of chlorobuspirone standard, accurately weighed to a 100 ml volumetric flask. Dissolve in and dilute to volume with water. Transfer 100 ± 2 mg of buspirone hydrochloride reference standard to a 100 ml volumetric flask. Pipet 5.0 ml of the chlorobuspirone standard solution into the flask. Dissolve in and dilute to volume with water - Standard Solution.

Sample Preparation

Transfer about 100 mg of sample, accurately weighed, to a 100 ml volumetric flask. Dissolve in and dilute to volume with water - Sample Solution.

Chromatographic Guidelines*

Instrument:	Any system capable of utilizing the specified column and having a detector capable of operating at 254 nm.
Column:	Alltech C_{18}, 25 cm x 4.6 mm ID or equivalent.
Mobile Phase:	Add 600 ml of acetonitrile to 400 ml of 0.01 M Phosphate Buffer (See pg. 10 assay, Reagent 7).
Flow Rate:	2.0 ml/min.
Range:	0.02 AUFS.
Wavelength:	254 nm.
Chart Speed:	0.25 cm/min.
Typical Retention Time:	11.3 min.

*Similar systems giving equal or better precision may be used.

Procedure

Chromatograph 25 microliter aliquots of the standard solution until the system is giving adequate chromatographs. Then chromatograph duplicate 25 microliter aliquots of the standard and sample solutions. Bracket each set of sample aliquotes with duplicate aliquots of standard.

Calculations

1. System Precision:

$$\% \text{ RSD} = \frac{100}{\bar{X}} \left[\frac{\sum_{i=1}^{n} (X_i - \bar{X})^2}{n-1} \right]^{\frac{1}{2}}$$

Where: X_i = Area of the individual standard peaks.

$\bar{X}$ = Average area of the standard peaks.

n = Number of standard peaks.

If the % relative standard deviation exceeds 5% the analysis must be repeated.

2. % Chlorobuspirone:

% Chlorobuspirone, w/w = $A/_B$ x $D/_C$ x E x 100.

Where:

A = peak area of chlorobuspirone in sample.

B = peak area of chlorobuspirone in standard.

C = sample wt. mg

D = standard wt., mg

E = factor = 0.05

1,4-Di(2-pyrimidinyl)piperazine dihydrochloride:

Internal Standard Preparation

Dissolve 25 mg of octacosane in 100 ml of chloroform - Internal Standard Solution.

Standard Preparation

Transfer about 10 mg of standard, accurately weighed, to a 100 ml volumetric flask. Dissolve in and dilute to volume with methanol. Pipet 10.0 ml of this solution into another 100 ml volumetric flask. Add by pipet 10.0 ml of internal standard solution, dilute to volume with chloroform and mix well - Standard Solution.

Sample Preparation

Transfer about 100 mg of sample, accurately weighed, to a 100 ml volumetric flask. Pipet 10.0 ml of methanol into the flask and swish to dissolve to sample. Pipet 10.0 ml of internal standard solution into the flask, dilute to volume with chloroform and mix well - Sample Solution.

Chromatography Guidelines*

Instrument:	Any instrument equipped with a flame ionization detector, recorder, capable of utilizing the specified column and capable of maintaining the specified temperature is suitable.
Column:	2 m x 2 mm ID glass coil with 3% OV-17 on 80/100 mesh Supelcoport.
Column Temp.:	250°C isothermal.
Injector Temp.:	250°C.
Detector Temp.:	300°C.
Carrier Gas:	Helium at 30 ml/min.
Chart Speed:	0.5 cm/min.
Typical Retention Times:	

1. Internal Standard - 3.2 minutes.
2. 1,4-Di(2-pyrimidinyl)piperazine dihydrochloride 2.1 minutes.

*Systems giving equal or better performance characteristics may be used.

System Resolution

Set the chart speed at 2 cm/min and inject 2 µl of the standard solution. Calculate the resolution factor between the standard and the internal standard as follows:

$$\text{Resolution Factor} = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

Where: t_1 = Retention time of the standard.

t_2 = Retention time of the internal standard.

W_1 = Width of the standard peak at the peak base, obtained by extrapolating the tangents of the inflection points of the peak sides to the baseline.

W_2 = Width of the internal standard peak at the peak base, obtained as for W_1.

If the resolution factor is not less than 2.0 then the system resolution is adequate.

Procedure

Chromatograph 2 microliter aliquots of the standard until the system has a satisfactory resolution factor and has stabilized. Then chromatograph duplicate 2 microliter aliquotes of the standard solution followed by duplicate 2 microliter aliquots of the sample solution. Again chromatograph duplicate 2 microliter aliquots of the standard solution. Repeat the sequence a second time.

Calculations

1. Calculate the response factor, R, for each injection:

$$R = \frac{\text{Peak area of the 1,4-DPPDH}}{\text{Peak area of the internal standard.}}$$

2. Calculate the % relative standard deviation, % RSD, for the injection of the standard solution:

$$\%RSD = \frac{100}{\bar{X}} \left[\frac{\sum_{i=1}^{n} (Xi - \bar{X})^2}{n-1} \right]^{\frac{1}{2}}$$

Where: Xi = The R value of any one injection of standard solution.

$\overline{X}$ = The average R value of all the standard injections (n).

n = The number of standard injections.

If the % RSD is greater than 5% the analysis must be repeated.

3. Calculate the % 1,4-di(2-pyrimidinyl)piperazine Dihydrochloride w/w, Z, for each sample using the average R value of each sample and standard.

$$Z = \frac{R\ sample}{R\ std} \times \frac{Std\ wt.\ (ug)}{10} \times \frac{100}{Sam\ wt.\ (mg)}$$

Report results to the nearest 0.1%.

Particle Size: Determine in accordance with the USP procedures for Powder Fineness, <811>, using 25 g. of sample and an 80 mesh screen.

Assay:

Reagents

1. 1 N Hydrochloric Acid: Dilute 8.5 ml of concentrated hydrochloric acid to 100 ml with distilled water.
2. Acetonitrile: HPLC grade.
3. Methanol: HPLC grade.
4. Potassium phosphate, monobasic ($K H_2PO_4$): AR.
5. Propyl Paraben RS.
6. Buspirone Hydrochloride RS.
7. Buffer Solution: Dissolve 1.36 g of monobasic potassium phosphate in distilled water and dilute to 1000 ml with distilled water. Adjust the pH of the solution to 7.5 using 10% w/v sodium hydroxide solution. Filter through a 0.45 micron Millipore Type HA (or equivalent) filter before use.

Internal Standard Preparation

Dissolve about 250 mg of propyl paraben RS in 100 ml of methanol. Pipet 25.0 ml of this solution into a 500 ml volumetric flask, dilute to volume with water and mix well - Internal Standard.

Standard Preparation

Transfer about 100 mg of buspirone HCL RS, accurately weighed, to a 200 ml volumetric flask. Add 50 ml of 1N hydrochloric acid and dilute to volume with water. Pipet 10.0 ml of this solution and 10.0 ml of internal standard solution into a 50 ml volumetric flask. Dilute to volume with water and mix well - Standard Solution.

Sample Preparation

Transfer about 100 mg of sample, accurately weighed, to a 200 ml volumetric flask. Add 50 ml of 1N Hydrochloric Acid and dilute to volume with water. Pipet 10.0 ml of this solution and 10.0 ml of internal standard solution into a 50 ml volumetric flask. Dilute to volume with water and mix well - Sample Solution.

Chromatographic Guidelines*

Instrument:	Any instrument capable of accepting the specified column, operating under the specified conditions and monitoring absorbance at 254 nm is acceptable.
Column:	Alltech C_{18}, 25 cm x 4.6 mm.
Mobile Phase:	Mix 400 ml of acetonitrile and 600 ml of buffer solution (reagent 7).
Flow Rate:	2.0 ml/min.
Chart Speed:	0.25 cm/min.
Typical Retnetion Times:	1. Buspirone HCl - 5.5 min. 2. Internal Std. - 3.0 min.

*Systems giving equal or better performance characteristics may be used.

Systems Suitability

1. System Resolution - Set the chart speed at 2 cm/min and chromatograph a 25 microliter aliquot of standard solution. Calculate the resolution factor as follows:

$$\text{Resolution Factor} = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

Where t_1 = Retention time of the internal standard.

t_2 = Retention time of the buspirone HCl.

W_1 = Width of the internal standard peak at the peak base, obtained by extrapolating the tangents of the inflextion points of the peak sides to the baseline.

W_2 = Width of the buspirone HCl peak at the peak base, obtained as for W_1.

Since the chart speed is 2 cm/min, the values obtained for W_1 and W_2 must be divided by 2.

If the resolution factor is not less than 4.0, the system resolution is adequate.

2. System Precision - 25 microliter aliquots of standard solution are chromatographed until duplicate injections have R values which agree within 2%, relative. When this condition has been met and the resolution factor is not less than 4.0 then the system is suitable for use.

Procedure

Chromatograph duplicate 25 microliter aliquots of standard and sample solution. At the end of the run and between every fourth sample again chromatograph duplicate 25 microliter aliquots of standard solution.

Calculations

1. Calculate the response factor, R, for each chromatogram:

$$R = \frac{\text{Peak area of the buspirone HCl}}{\text{Peak area of the internal standard.}}$$

2. Calculate the % realtive standard deviation, % RSD, for the standard injections:

$$\%RSD = \frac{100}{\bar{X}} \left[\frac{\sum_{i=1}^{n} (Xi - \bar{X})^2}{n-1} \right]^{\frac{1}{2}}$$

Where: X_i = The R value of any one injection of the standard solution.

$\bar{X}$ = The average R value for n injections of the standard solution.

n = The number of injections of standard solutions.

If the % RSD exceeds 2.0%, the system precision stability throughout the run was not acceptable and the analysis must be repeated.

3. Calculate the % buspirone HCl in the samples using the average R values for the sample and standard

$$\% \text{ Buspirone HCl} = \frac{R \text{ sam}}{R \text{ std}} \times \frac{\text{std wt (mg)}}{\text{sam wt (mg)}} \times 100.$$

Report the result to the nearest 0.1%.

CORRSPONDENCE-

E0020.12

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812) 429-5000
Direct Line: (812) 429-5589

April 26, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUKG-B0488-0052 submitted under the requirements of 21 CFR 314.80(c)(1)(i) as a fifteen-day "Alert Report".

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

1988 MAY -2 PM 6:54
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FOR DRUGS & BIOLOGICS

DFM/ab

Attachment

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HFN-120
FOR DRUGS & BIOLOGICS

E 1867

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

March 30, 1988

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

REFERENCES: 1. NDA #18-731, BUSPAR® Tablets
2. Initial Drug Experience Report
Submitted to Reference 1,
March 10, 1988 (pages E1865 - E1866)

Gentlemen:

In accordance with 21 CFR 314.80 (c)(1)(i), we submit follow-up information (pages E1868 - E1869) and a copy of Reference 2 (pages E1870 - E1871) for a drug experience report identified in our files as SRUSA-M0388-0017.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

OIG REPORTS

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

1862

March 10, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Dr., Room 214
Rockville, MD 20857

REFERENCE: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of two initial drug experience reports identified in our files as SRUSA-M0388-006 and SRUSA-M0388-0017, submitted under the requirements of 21 CFR 314.80(c)(1)(i) as fifteen-day "Alert Reports".

If you have any questions or comments concerning these reports, please contact me.

Sincerely,

BRISTOL-MYERS
U. S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/dh

Attachment

F 1857

REPORTS

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

March 4, 1988

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

REFERENCES: 1. NDA #18-731, BUSPAR® Tablets
2. Initial Drug Experience Report Submitted to Reference 1, February 18, 1988 (pages E1852 - E1853)

Gentlemen:

In accordance with 21 CFR 314.80 (c)(1)(i), we submit follow-up information (pages E1858 - E1859) and a copy of Reference 2 (pages E1860 - E1861) for a drug experience report identified in our files as SRUSA-M0285-0005.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

DRUG REPORTS]

A 2072

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

February 25, 1988

Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics
Document Control Room #10B-30
HFN-120
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REFERENCES: 1) NDA 18-731 for BuSPAR® 5 and 10 mg tablets
2) Annual Report to this NDA, dated October 30, 1987

Gentlemen:

The first Annual Report for the BUSPAR NDA was submitted to the Division on October 30, 1987; however, several stability study reports dealing with the drug substance were inadvertently omitted from that submission.

Accordingly, we provide here the omitted reports listed below:

Accession No.	Title	Page
BRAC-AL-09315	Stability of Buspirone HCl, Lot 16, Raw Material Sealed in Glass Vials	A 2074
BRAC-AL-09316	Stability of Buspirone HCl, Lot 19, Raw Material Sealed in Glass Vials	A 2079
GWOZ-EJ-09699	The Stability of Product 09022-001-23 Using Buspirone HCl Supplied by Ganes Co.	A 2084
GWOZ-EJ-09834	The Stability of MJ 9022-1 Raw Material, Lot 31.	A 2100
GWOZ-EJ-09835	The Stability of MJ 9022-1 Raw Material, Lot 25.	A 2106
SCHE-BR-10958	Stability of Buspirone HCl, Lot 37, Drug Substance.	A 2112
SCHE-BR-11812	The Stability of MJ 9022-1, Lot 42, Drug Substance in Low Density Polyethylene Bags.	A 2116

These reports contain no information or data which would affect BUSPAR labeling or suggest diminished safety or efficacy of BUSPAR 5 and 10 mg tablets.

We regret any inconvenience this oversight may have caused the Division.

Sincerely

BRISTOL S
U. S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/sg

Attachment

ORIG

REPORTS
E 1854

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

February 19, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUSA-M0288-0059 submitted under the requirements of 21 CFR 314.80(c)(1)(i) as a fifteen-day "Alert Report".

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

120

CRIG

E 1851

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812) 429-5000
Direct Line: (812) 429-5589

February 18, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUSA-M0288-0005 submitted under the requirements of 21 CFR 314.80(c)(1)(i) as a fifteen-day "Alert Report".

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

—120 ORIG

E 1848 REPORTS

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

February 17, 1988

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

REFERENCES: 1. NDA #18-731, BUSPAR® Tablets
2. Initial Drug Experience Report Submitted to Reference 1, July 23, 1987 (page E1464)

Gentlemen:

In accordance with 21 CFR 314.80 (c)(1)(i), we submit follow-up information (page E1849) and a copy of Reference 2 (page E1850) for a drug experience report identified in our files as SRUSA-M0787-0055.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

Orig

REPORTS
E001843

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812) 429-5000
Direct Line: (812) 429-5589

January 28, 1988

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

RECEIVED
DIVISION OF DRUG AND
BIOLOGICAL PRODUCT EXPER.
1988 FEB -2 AM 12:32

REFERENCES: 1) NDA #18-731, BUSPAR® Tablets
2) Initial Drug Experience Report Submitted to Reference 1, October 21, 1987 (page E1661)
3) Follow-up Information, submitted December 23, 1987 (pages E1678-1679)
4) Telephone conversation between David Barash and Duane Morrow, January 12, 1988

Gentlemen:

In accordance with 21 CFR 314.80 (c)(1)(i) and the telephone conversation (reference 4), we submit additional follow-up information (page E1844) and copies of References 2 & 3 (pages E1845 - E1847) for a drug experience report identified in our files as SRUSA-M1087-0052.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

RECEIVED
NATIONAL CENTER
FEB 04 1988
HFN-120
FOR DRUGS & BIOLOGICS

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Attachment

REPORTS
1839

BRISTOL-MYERS
U.S PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

January 27, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Dr., Room 214
Rockville, MD 20857

REFERENCE: 1) NDA 18-731, BUSPAR Tablets
2) Initial Drug Experience Report
Submitted to Reference 1,
January 19, 1988 (not a 15-day report)

Gentlemen:

In accordance with 21 CFR 314.80(c)(1)(i), we submit information and a copy of Reference 2 for the drug experience report identified in our files as SRUSA-M1287-0048. The initial report was not submitted as a 15-day report. Recently received new information has caused this report to be changed to a 15-day.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U. S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/dh

Attachment

Orig

REPORTS
1834

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812) 429-5000
Direct Line: (812) 429-5589

January 21, 1988

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of two initial drug experience reports identified in our files as SRUSA-M0188-0015 and SRUSA-M0188-0052, submitted under the requirements of 21 CFR 314.80(c)(1)(i) as fifteen-day "Alert Reports".

If you have any questions or comments concerning these reports, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

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RECEIVED
DIVISION OF DRUG AND
BIOLOGICAL PRODUCT EXPER.
1988 JAN 27 AM 12: 33

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NATIONAL
CENTER
FEB 04 1988
HFN-120
FOR DRUGS &
BIOLOGICS

REVIEW AND EVALUATION OF CLINICAL DATA
NDA 18-731

Sponsor: Bristol-Myers

Drug: Buspirone (BuSpar^{R})

FEB 19 1988

Drug Category: Anxiolytic

Material Submitted: Periodic ADR Report covering the quarter 10/1/87 - 12/31/87. Included are 89 initial reports and follow-up on 23 reports.

Correspondence Date: January 19, 1988

Date Received: January 27, 1988

I. Reported Events

A. Cardiovascular

There were three reports of tachycardia, two of which abated when buspirone was discontinued. The third was associated with a headache and concurrent tapering of alprazolam; it abated shortly after each dose. There was one report of palpitations and another physician noted that he saw an "unusually high incidence of palpitations". A physician who took a single dose experienced a pounding pulse and a mild stimulant effect.

There were three other cardiovascular events which are not readily attributable to buspirone. A 32 year male was noted to have irregular PVCs after about 6 months on buspirone 25 mg/day; he had no prior history of similar symptoms and no history of cardiovascular disease. It was noted that the frequency of the PVCs decreased over time in spite of continued treatment. An ECG of a 45 year old man on buspirone 30-40 mg/day for several months, who was also treated with haloperidol for Tourette's Syndrome, showed intraventricular conduction delay with left anterior hemiblock. There was one report of CHF with no further information given.

B. CNS

There were five reports of marked sedation or significant drowsiness. In addition, one lay person reported feeling "light, airy, floating." There were five reports of dizziness or vertigo. One was associated with confusion nausea, dry mouth, disorientation, muscle aches, and headache, however, this 57 year old woman on 40 mg/day for two days was concurrently receiving Premarin, Synthroid, amitryptiline, and Halcion. Another of the cases was associated with dry mouth and discomfort. One physician noted that "most of his patients are experiencing dizziness."

Some form of nervousness or increased anxiety was reported in four patients. A 40 year old woman with a history of benzodiazepine abuse, on 30 mg/day for 7 days, experienced increased anxiety, depersonalization, nightmares, eye lid fluttering, onset of phobic symptoms and memory problems. The acute symptoms resolved however the phobia and episodic severe anxiety persist. A male experienced marked anxiety about 40 minutes after a single 5 mg dose. After 15 mg/day for 4 days, a male experienced nervousness, nausea and lightheadedness. A woman who had been taking chlorazepate "for years" complained of anxiety, nervousnessness, painful urination, loud sounds and skin pain. One physician noted that "many patients" initially on buspirone 30 mg/day became extremely nervous when the dose was increased to 40 mg/day; another noted that 50% of his patients complained of "jitteriness and coffee nerves".

A 38 year old drug abuser took daily doses of 50 - 100 mg because "she feels the need to get high"; she was also on other medications and alcohol and experienced periodic confusion.

One patient on multiple concurrent medications (theophylline, Brethine, ranitidine, Transderm-nitro, Naldecon, Nasalcrom, and Calan) experienced hallucinations, frightful nightmares, tingling over whole body and loss of balance.

A 23 year old female with a history of generalized motor seizures associated with benzodiazepine and cocaine abuse also seized while on buspirone 30 mg/day for one month. Urine screening indicated that she had been free of drug abuse for over 3 months. She was concurrently on desipramine.

C. EENT

There were two reports of tinnitus, however, one was subsequently attributed to a viral infection. A 26 year old female on 20 mg/day for 14 days developed optical photosensitivity which abated when buspirone was discontinued. A 64 year old male experienced a pressure in his ear for 15 minutes after each dose.

D. Endocrine

There was one report of galactorrhea in a woman.

E. Gastrointestinal

There was one report each of increased and decreased appetite.

F. Genitourinary

There was one report of urinary retention at a daily dose of 30 mg; it abated with discontinuation.

G. Musculoskeletal

There were three reports of muscle aches or pains; one of the reports was by a man with Parkinson's disease and pre-existing muscle pain. Two patients discontinued treatment with buspirone due to joint pain.

H. Neurological

There were three reactions which could be categorized as extrapyramidal syndromes. One 30 year old female had a "marked" dystonic reaction on her second day of therapy. A 67 year old woman experienced muscle rigidity, however, she was concomitantly on thioridazine 25 mg/day. A 33 year old male experienced restlessness, shakiness, and frequent urination after two months of treatment. The reaction was successfully treated with Cogentin.

There was one report of numbness of the entire side of the body and there were two reports of "electrical jolts".

I. Skin/Allergic Type Reactions

There were three reports of hair loss, two specified to occur in young women. One of the women was concurrently on Accutane. There were seven reports of allergic reactions manifested by rash. Other associated symptoms were scratchy throat, pruritic vesicles, hives and possible photosensitization.

J. Miscellaneous

Four cases involved either abrupt discontinuation of a benzodiazepine or a taper immediately prior to onset. The multiple complaints could reasonably be attributed to withdrawal. A 45 year old woman experienced polyuria and back pain three days after trazodone and alprazolam 0.75mg/day were stopped; these improved when the buspirone was discontinued and her previous regimen was restarted. Another woman experienced nervousness, palpitations, and headache; her diazepam 10 mg/day was discontinued one week prior. One day after stopping Aventyl, alprazolam and hydroxyzine, a male experienced middle insomnia. A 44 year old woman with a diagnosis of agoraphobia was tapered off Valium which she had been taking for 10 years. She felt "out of it", in a stupor and experienced marked anxiety of sufficient severity to be seen in an emergency room. When Valium was restarted, the symptoms rapidly abated.

There were several miscellaneous reactions. One physician reported that "patients" had vascular headaches, GI pain, muscle twitching or increased urination. Another physician reported that 6 of 8 patients who were taking theophylline experienced nervousness and jitteriness when 15 mg buspirone was added; the reaction abated when buspirone was discontinued.

Five reactions were reported to involve the liver. Two of these stated "liver problems". In one patient "liver enzymes were noted to increase and then to decrease to normal levels when buspirone was discontinued. SGPT increased to 104 in a 36 year old male with a history of MDD, low back pain and alcohol abuse. He had been on buspirone 20 mg/day for 29 days and denied alcohol use during this time. The SGPT levels remained elevated, ranging from 95 to 180 over a 2 months period and then returned to normal. Hepatitis A and B antigens were negative. A 31 year old male, who works in the pest control business and recently had elevated cholinesterase levels, also experienced a mild elevation of SGOT (49) and SGPT (129). He had been on buspirone and doxepin for 5 months.

Cholesterol and triglyceride levels were noted to be elevated in a 49 year old male on 15 mg buspirone/day for 21 days: cholesterol increased from a baseline of 230 to 360 and triglycerides increased from 173 to 980. These are difficult to interpret without ascertaining the timing in relation to meals and meal composition.

Prothrombin time was noted to be increased in one patient.

Two elderly females (73 and 81 years of age) felt burning sensations. One experienced the pain in both legs over a 3 month period wherein she was also treated with antibiotics (UTI) and temazepam. The other, who had Alzheimer's Disease, felt it over her entire body

One woman experienced dysphoria and a headache, another complained of a "strange body odor", a third was noted to have erythema of the marginal gingiva, and a fourth felt cold sensations on her back. The two final reports were in post-operative patients. One 80 year old woman who became psychotic on scopalamine, became increasingly anxious and agitated when buspirone was added to lorazepam; she was also noted to have involuntary movements and posturing. The other man was noted to have difficulty with speech and reading however subsequent follow-up indicated that he had two small emboli.

K. Overdose

There were two reports of overdose with no adverse sequelae other than drowsiness. A two year old boy ingested 10 mg of buspirone along with 50 mg imipramine and 10 mg Isordil. The second overdose involved an unknown dose.

II. Discussion

All adverse events in this Periodic Report are already currently labeled or have been recommended for inclusion in a new Post-Introduction Reports section. I note that there is another report of increased prothrombin time. We should also be alert to the possibility of an interaction between buspirone and theophylline. One physician noted jitteriness in 6 of 8 patients on the combination which could be evidence of increased theophylline levels. Another patient on both theophylline and buspirone experienced several adverse events, however, the case is difficult to evaluate because the patient was concurrently on several other drugs. No action is indicated as a result of this Period ADR Report.

Karin A. Kook, Pharm.D.

cc:
Orig:NDA18-731
HFN-120
HFN-120/TLaughren
KKook
ft/kk/2/17/88

2-18-88

I agree with the above recommendation

T. Laughren

(5)

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812) 429-5000
Direct Line: (812) 429-5589

January 19, 1988

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

This submission complies with 21 CFR 314.80(c)(2) for the periodic reporting of adverse drug experiences. The period covered by this report is October 1 - December 31, 1987. The report includes 89 initial reports and 23 follow-up reports.

If you have any questions concerning the information in this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

ORIGINAL

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

December 11. 1987

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUSA-M1287-0040, submitted under the requirements of 21 CFR 314.80(c)(1)(i) as fifteen-day "Alert Reports".

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

GILEAD

REPORTS
E001677

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

December 23, 1987

Food and Drug Administration
Central Document Room
Parklawn Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

REFERENCES: 1. NDA #18-731, BUSPAR® Tablets
2. Initial Drug Experience Report Submitted to Reference 1, October 21, 1987 (page E1661)

Gentlemen:

In accordance with 21 CFR 314.80 (c)(1)(i), we submit follow-up information (pages E1678-E1679) and a copy of Reference 2 (page E1680) for a drug experience report identified in our files as SRUSA-M1087-0052.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

1987 DEC 31 11:12:57

E001674

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

December 23, 1987

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUSA-M1087-0077, submitted under the requirements of 21 CFR 314.80(c)(1)(i) as fifteen-day "Alert Reports". It is being submitted at this late date because we only recently received additional information regarding the hospitalization of the patient.

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

E001681

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

December 24, 1987

Central Document Room
Center for Drugs & Biologics
Food and Drug Administration
12420 Parklawn Drive, Room 214
Rockville, MD 20857

Reference: NDA #18-731, BUSPAR® Tablets

Gentlemen:

Attached are the known details of an initial drug experience report identified in our files as SRUSA-M1087-0080, submitted under the requirements of 21 CFR 314.80(c)(1)(i) as fifteen-day "Alert Reports".

If you have any questions or comments concerning this report, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

Attachment

CLINICAL INVEST.

CLINICAL INVESTIGATORS

Harold Goldberg, M.D. Boston State Hospital,
Boston, MA 02124

Karl Rickels, M.D., University Hospital,
Philadelphia, PA 19104

John P. Feighner, M.D., , P.O. Box 1660, La Mesa,
CA 92041

Ward Smith, M.D., , 2212 Lloyd Center, Portland,
OR 97232

Louis Fabre, Jr., Ph.D., M.D., , Research
Testing, Inc., Houston, TX 77004

Burton Goldstein, M.D., . Department of Psychiatry,
University of Miami School of Medicine, P.O. Box 016960, Miami,
FL 33101

Jerry Rodos, D.O., University of New England,
New England College of Osteopathic Medicine, Biddeford, MA 04005

Charles Bowden, M.D., , University of Texas Health
Sciences Center, San Antonio, TX 78284

Jay B. Cohn, M.D., Ph.D. , University of California
at Irvine, Irvine, CA 92712

John D. Arnold, M.D.,), Harry S. Truman Research Laboratory, Kansas City, MO 64108

Samuel Gershon, M.D. Lafayette Clinic, Detroit, MI

Richard J. Finnerty, Ph.D., Boston State Hospital, Boston, MA 02124

Ernest Hartmann, M.D.,), Boston State Hospital, Boston, MA 02124

Rubin Bressler, M.D.,
University of Arizona Medical Center, Tucson, Arizona 85724

Albert Cohen. M.D.,
Peninsular Testing Corporation, Miami, FL

Joseph Shannon, M.D.,
Southern California Research Institute, Los Angeles, CA 90045

I Herbert A. Moskowitz, Ph.D.,
Southern California Research Institute, Los Angeles, CA 90045

M. Linnoila, M.D., Ph.D. and C. W. Erwin, M.D.,
Duke University Medical Center, Durham, NC 27710

Malcolm H. Lader, D.Sc., Ph.D.. M.D., F.R.C. Psych. and Alyson Bond, Ph.D.), Department of Pharmacology, Institute of Psychiatry, University of London, U.K.

Mauri J. Mattila, M.D.
Department of Pharmacology, University of Helsinki, Helsinki, Finland

Herbert Meltzer, M.D., Illinois State Psychiatric Institute, Chicago, IL 60612

Timo Seppala, M.D. and Tapio Ranta, M.D.,
Departments of Pharmacology and Biochemistry, University of Helsinki, Helsinki, Finland

Jonathan O. Cole, M.D. and Maressa H. Orzack,),
Psychopharmaoclogy Unit, McLean Hospital - Harvard Medical School, Belmont, MA 02178

John D. Griffith, M.D., , Houston VA Medical Center, Houston, TX

SUPPLEMENTS

NDA 18-731/S-002

Bristol-Myers Company
Attention: Walter A. Zygmunt, Ph.D.
Regulatory Affairs
Evansville, Indiana, 47721

OCT 30 1986

Dear Dr. Zygmunt:

We acknowlege the receipt on October 14, 1986, of your communication dated October 14, 1986, regarding your supplemental new drug application (NDA 18-731 /S-002) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for BuSpar® (buspirone hydrochloride), tablets.

The supplemental provides for final printed labeling (container labels) for bottles of BuSpar® (100's) in 5 mg and 10 mg tablets, professional sample bottles of 3 mg and 5mg tablets, individual container cartons for professional sample bottles of 3mg and 5mg tablets, and cartons for patient starter kits containing two packages of sample bottles of 3mg and 5mg.

We have completed our review of this submission and we have the following comments:

All immediate container labels should be revised to include the statment: "Each tablet contains (quantity of active ingredient) buspirone hydrochloride." and the HOW SUPPLIED section of the package insert should be revised to replace the statements: "Store at Room Temperature - Protect from Temperatures greater than 86°F (30°C). Dispense in a tight, light-resistant container (USP)."

Please submit twelve copies of the revised final printed labeling when it is available. This submission should be designated for administrative purposes an "FPL Supplement" to the approved NDA 18-731. Approval of the supplement by The FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of that labeling may be required.

If you have any questions please contact, Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-4020.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Offic of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig:NDA
HFN-120
HFN-120/PLeber/TLaughren/KKook
FZinsitz/RShultz
ADeCicco
ad/rd/10/27/86

DOC 0333c
PERMITTED

NDA 18-731

Bristol-Myers Company
Attention: Frank W. Furth, M.D.
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

OCT 21 1986

Dear Dr. Furth:

Please refer to your new drug application dated December 18, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation BuSpar® (buspirone hydrochloride) tablets, NDA 18-731.

Please also refer to your September 29, 1986 submission containing final printed labeling. We have completed our review of this submission and it is approved. However, we recommend a change in the ADVERSE REACTIONS section, involving the second sentence in the subsection labeled "Associated with Discontinuation of Treatment. We suggest that you replace that sentence with the following:

> "Approximately 10% of the 2200 anxious patients who participated in the Buspar® premarketing clinical efficacy trials discontinued treatment due to an adverse event. These were mostly three to four week studies, but also included approximately 700 patients in long term studies."

Please make the above change (or suggest an alternative) to be done at the next printing. Our letter of September 29, 1986 detailed the conditions relating to the approval of this application.

If you have any questions please contact, Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-4020.

Sincerely yours,

18-L-10-20-EC

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig:NDA
HFN-120
HFN-120/PLeber/TLaughren
WHeydorn/JContrera
FZinsitz/RShultz
ADeCicco
HFN-226/MYau
HFN-713/ENevious
ad/rd/10/17/86/ft/10/20/86

DOC 0318c
APPROVAL OF FPL
(Package Insert)

19.1

NDA 18-731/S-011

Bristol-Myers U.S. Pharmaceutical Group
Attention: Duane F. Morrow, Ph.D.
Evansville, Indiana 47721-0001

APR 6 1988

Dear Dr. Morrow:

Please refer to your supplemental new drug application dated October 5, 1987 submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for BuSpar (buspirone hydrochloride) Tablets. We also refer to your amendment to the supplemental application dated December 16, 1987.

The amendment of the supplemental application provides your response to our letter of November 13, 1987, in which we requested that the terms "cogwheel rigidity" and "tunnel vision" be included in the labeling for BuSpar. You have agreed with the inclusion of the term "tunnel vision" but disagreed with the need for the term "cogwheel rigidity."

We have completed our review of this supplemental application and we continue to consider the term "cogwheel rigidity" to be appropriate for inclusion in the label. There is no minimal number of cases required for inclusion of an event in the labeling. The only criterion for including an adverse reaction is that it be "reasonably associated with the use of the drug," (21 CFR 201.57). The case of cogwheel rigidity in question appears reasonably associated with the use of buspirone: its onset was associated with an increase in dose and it abated when the dose was decreased. It is true that it did not recur with a subsequent increase, however, tolerance to such adverse events has been noted. In addition, given other adverse effects associated with the extrapyramidal system, it is reasonable to anticipate that cogwheel rigidity would be observed. Furthermore, an additional patient (1087-0052) was noted on follow-up to have cogwheel rigidity.

Please submit final printed labeling with these terms included in the Adverse Reactions section. This change can be made under 21 CFR 314.70(c), Changes Being Effected.

If you have any questions concerning this NDA, please contact Dr. Richard Potter, Consumer Safety Officer, at (301) 443-5030.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research

cc: ORIG NDA
HFN-120
HFN-120/Potter
Kook/Laughren
Leber
rd/rp/4/1/88
Doc # 2733c
SUPPLEMENT APPROVABLE

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-731

MAR 28 1988

Sponsor: Bristol-Myers

Drug: Buspirone (BuSpar^{R})

Drug Category: Anxiolytic

Material Submitted: Response to Requested Label Change (letter dated November 13, 1987)

Correspondence Date: December 10, 1987

Date Received: December 16, 1987

I. Sponsor's Response:

We requested that "cogwheel rigidity" and "tunnel vision" be included in the new "Post-Introduction Clinical Experience" section. Bristol-Myers states that they include new events when four or more reports have been received. Although there have been only three reports of "tunnel vision," they have agreed to include the term. They state, however, that they do not wish to add "cogwheel rigidity" because there has only been one reported case. They also state that newly received follow-up information reveals that the symptom abated when the dosage was lowered from 30mg/day to 15/mg/day. There was no re-occurrence of objective rigidity when the dose was subsequently increased again even though the patient had a subjective sense of rigidity.

II. Discussion

There is no minimal number required for an event's inclusion in labeling; the only provision for including an ADR is that it be "reasonably associated with the use of the drug." Thus, even a single report is an adequate basis for requesting a change in the label.

The case of cogwheel rigidity in question appears reasonably associated with the use of buspirone: its onset was associated with an increase in dose and it abated when the dose was decreased. It is true that it did not recur with a subsequent increase, however, tolerance to such adverse events has been noted. In addition, given other adverse effects associated with the extrapyramidal system, it is reasonable to anticipate that cogwheel

rigidity would also be observed. I also note that an additional patient (1087-0052) was noted on follow up to have 1+ cogwheel rigidity of the wrists/elbows and 2+-3+ in the neck/shoulders. The primary reaction which prompted the report was dystonia. The reaction resolved with Cogentin and discontinuation of buspirone.

III. Recommendation

The sponsor should be informed that we continue to recommend the inclusion of cogwheel rigidity as a Post-Introduction Event.

Karin A. Kook, Ph.D.

Q4C-7

A002068

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

December 10, 1987

Division of Neuropharmacological
Drug Products
HFN-120
Office of Drug Research and Review
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Reference: 1) NDA #18-731/S-011; BUSPAR® Tablets
2) Letter from Paul Leber to Duane Morrow, November 13, 1987

Gentlemen:

The letter from Dr. Leber of November 13, 1987 requested that the terms "cogwheel rigidity" and "tunnel vision" be included in the "POST-INTRODUCTION CLINICAL EXPERIENCE" section of the BUSPAR labeling. Bristol-Myers had originally selected a cut-off value of four reports of any given ADE occurring between the time of launch (December, 1986) and September, 1987 to select the ADEs to be included in the revised labeling submitted in S-011 on October 5, 1987. This cut-off value was intended to reflect an estimated ADE incidence of approximately 1 in every 100,000 new BUSPAR therapy starts. Because there have been three reports of tunnel vision in that time, reflecting only a slightly lower frequency of occurrence, we agree that the addition of this ADE to the labeling is acceptable.

However, to date we have received only one report of "cog-wheel rigidity". The fact that there has been only this one report, from an estimated 423,000 patients receiving prescriptions for BUSPAR thus far, argues against the inclusion of "cog-wheel rigidity" in the BUSPAR labeling. It is also important to note that additional information recently obtained from the reporting physician indicates that this finding abated after lowering the dosage of BUSPAR from 30 mg/day back to 15 mg/day, and did not reappear upon increasing the dose back to 30 mg/day. The physician stated that this patient is still on BUSPAR therapy. The patient's course over time suggests some features are present here which differ from those which might be expected from more typical cases such as those induced by antipsychotic drugs. (The follow-up ADE report containing this new information is being routinely submitted in the next BUSPAR quarterly ADE report, and a copy of the 1639 form is included with this letter as Attachment 1).

It seems highly inappropriate to us to make this one case report with a somewhat atypical course the basis for an addition to the BUSPAR labeling at this time. Such a policy, if carried out diligently, would result in serious "over-labeling" of BUSPAR or any other drug.

Bristol-Myers is alert to new ADEs of this nature. If additional reports of "cog-wheel rigidity" come to our attention, you are assured that Bristol-Myers will quickly take appropriate action.

Please let me know if you are in agreement with this position, and we will then incorporate "tunnel-vision" into the labeling copy sent you on October 5, 1987, and have final printed labeling prepared.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs

DFM/ab

March 17, 1988

Duane F. Morrow, Ph.D.
Associate Director
Regulatory Affairs
Bristol-Myers
U.S. Pharmaceutical Group
Evansville, Indiana 47721-0001

Dear Dr. Morrow:

This is in response to your letter of March 8, 1988 and continues our dialogue concerning certain promotional claims for BuSpar, NDA 18-731.

We have read your proposed modifications to promotional claims previously discussed and find them acceptable at this time. We appreciate your firm's cooperation. However, we find it necessary to clarify one point further.

Your letter notes that you believe it "...misleading to both physicians and patients to imply that BuSpar is responsible for (the) 10% incidence of drowsiness." We assume that your belief is based upon the inability to absolutely determine the cause of this drowsiness, i.e. drug effect versus placebo. For the very same reason we believe it potentially misleading to suggest that the drug is definitely not responsible for this adverse reaction. Simply, there is no way to ascertain the actual causation. However, as noted above we do find your proposed remedy, provision of both drug and placebo incidence rates, as an acceptable method of offering this information.

It may interest you to know that an analogous situation was recently faced with the sponsor of an antihistamine drug product. Our position was identical in that matter. We trust that you find our clarification to be meaningful.

Sincerely yours,

Arthur K. Yellin
Assistant to the Director
Division of Drug Advertising
and Labeling
Office of Drug Standards

AKYellin:na 3/16/88
cc: HFN-240, HFA-224
ORIG(HFN-120, NDA 18-731)
2574z

21.1

ORIG

B 2128

SCS 012 AC
NDA SUPPL AMENDMENT
SCS 013 AC

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000
Direct Line: (812) 429-5589

April 12, 1988

Division of Neuropharmacological
Drug Products
Office of Drug Reseach and Review
Center for Drugs and Biologics
Document Control Room #10B-30
HFN-120
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

References: 1) NDA 18-731, BUSPAR Tablets (buspirone hydrochloride)
2) Supplemental new drug application dated October 12, 1987 (S-012, S-013)
3) FDA letter; P. Leber, M.D. to D. F. Morrow dated December 10, 1987 re reference 2.

ATTN: Paul Leber, M.D.

Gentlemen:

The purpose of this submission is to respond to your letter of December 10, 1987 (reference 3). A copy of the letter is enclosed. The accompanying narrative addresses all of the items (1 through 5) of that letter.

Should you have additional questions about the issues discussed or the information provided, please contact me.

Sincerely,

BRISTOL-MYERS
U.S. PHARMACEUTICAL GROUP

Duane F. Morrow

Duane F. Morrow, Ph.D.
Associate Director,
Regulatory Affairs

RECEIVED
NATIONAL CENTER
APR 20 1988
HFN-120
FOOD DRUGS & BIOLOGICS

DFM/sg
enclosures

18-731

January 13, 1988

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Marygale Ritzert
Director, Regulatory Affairs
Mead Johnson Division
Bristol-Myers U.S. Pharmaceutical Group
2400 Pennsylvania Street
Evansville, Indiana 47721-0001

Dear Ms. Ritzert

This is in reference to several promotional labeling materials for BuSpar (buspirone HCl) which have come to our attention through a complaint to Commissioner Young and through routine monitoring by the Drug Advertising Regulation Branch. The first, a direct mailing, features an air traffic controller, and is identified as J-D 130-D-87. Other materials addressed by this letter include J-F45 (a patient information brochure), J-3116-3-87 (a price list) and MJL 74207 (a journal advertisement).

While we note that although the text of the first piece follows introductory materials cleared through this Division, we do object to the scenario depicted for two reasons.

1. We have consistently objected to promotional campaigns for anxiolytic agents which represent and/or suggest use of such drugs for the treatment of every day stress, be it due to job pressures or to anxiety generated in the normal home environment. We feel that your choice of a high pressure occupation is inappropriate for suggestion of proper patient selection for BuSpar therapy.

2. Your choice of this particular occupational group is also objectionable in that Federal Aviation Administration regulations would specifically prohibit an employee taking an anxiolytic agent from performing direct air traffic control duties.

With respect to the patient information brochure and the price list, the first is regarded to be false, thereby misbranding the product under section 502(a) of the Federal Food, Drug and Cosmetic Act, in that under item #3 (Side Effects of BuSpar) the brochure states that "The three most commonly reported side effects in patients who have taken BuSpar are dizziness, nausea, and headache." The approved labeling for BuSpar notes that the second most commonly experienced side effect in controlled clinical trials was drowsiness, with an occurrence rate of 10%. While this rate was not statistically different from the drowsiness experienced by patients given placebo, it is inappropriate to subtract the placebo figure and/or to suggest that drowsiness did not occur. This applies to the claim found in the section of this brochure entitled "What Type of Medication is BuSpar?" The statement, "BuSpar does not usually produce

side effects such as drowsiness or physical or mental impairment that can make it difficult for you to go about your normal daily activities during treatment" contradicts the admonition in the approved labeling that patients newly placed on BuSpar therapy should "... not drive a car or operate potentially dangerous machinery" (until patients experience how this medication affects them)." The presence of this information on the following page does not alleviate the objection to the referenced claim. We would not object to mention that the drug associated drowsiness occurs with about the same frequency as placebo, provided that the actual rate for both (i.e. 10% and 3% respectively) is clearly stated in the claim.

The price list is violative in that it fails to provide full prescribing information as required and is not a "reminder labeling" piece under 21 CFR 201.100(f) since the piece makes numerous representations and suggestions regarding the safety and efficacy of the product. We also request that future printings include the actual incidence of drowsiness (10%) as above. Again, with inclusion of this information we have no objection to the statement "No more drowsiness than placebo."

We also note that the text of several of the referenced materials prominently feature a listing of "the most common adverse effects" experienced during clinical trials with BuSpar. This listing omits "Drowsiness (10%)." This was an oversight during review of the introductory promotional materials and should be included in all future materials. Based upon information available to date, as noted above, we continue to have no objections to claims that BuSpar exhibits no more drowsiness than placebo provided that the actual rate of occurrence of drowsiness for both groups observed in clinical trials is prominently featured.

The journal advertisement, MJL 74207, is regarded to be violative under section 502(n) of the Act in that it represents and suggests that BuSpar is devoid of psychomotor impairment based upon a study conducted in a limited number of normal volunteers.

We note and appreciate your immediate cancellation of the piece identified as J-D 180-9-87 by your own action when made aware of the complaints in the press. Your written response, within ten working days of receipt of this letter, should indicate your firm's intentions with respect to modification of future promotional materials for BuSpar in order to obviate recurrence of these violations. Your letter should also indicate the steps that you will take to discontinue use of the violative pieces identified herein as well as any similar or related promotional materials.

Sincerely yours,

Arthur K. Yellin
Assistant to the Director
Division of Drug Advertising
and Labeling
Office of Drug Standards

AKYellin:12/8/87:12/10/87:1/12/88(F)
cc: HF-1
HFN-1 (Dr. Peck)
[redacted] (Dr. Leber)
HFN-100 (Dr. Temple)
HFN-200 (Dr. Rheinstein)
HFN-240, HFA-224

K. Fratto 1/13/88

NDA 15731

Pharmacia

GENERAL CONTINUATION SHEET	PRODUCT Buspar Tablets	SAMPLE NO. 47926

I.R. Identification of Buspirone · HCl

The samples and standard spectrums of Buspirone HCl show a confirmed identification.

Calc. Checked
7-15-82
OJD

ANALYST(S) Robert E Sutton	ANALYST NO. 875	PAGE 1 OF ____ PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

47926
6/28/82

Confirmation of presence of Buspirone HCl in Buspar Tablets by Infared Spectroscopy

Ten (10 mg) milligram Tablets. (B 637)
20 tablets ground to a fine powder with a mortar and pestle.
20 tablets → 50 ml $CHCl_3$ Filtered thru Whatman #1 and Evaporated using Rotary evaporator → 10 ml $CHCl_3$.

Reference standard. Buspirone HCl MJ9022-1
MMJM266 1G. - EXP. 10/83

wt container + std	9.9844 gm
wt Container	9.7817 gm
wt of Std Buspirone HCl	0.2027 gm → 10 ml $CHCl_3$

40 5mg tablets ground to a fine powder with a mortar and pestle.

40 tablets → 50 ml $CHCl_3$ then filtered thru Whatman #1 and evaporated using a Rotary Evaporator → 10 ml $CHCl_3$.

The I.R. Spectrum of both samples and standard shows a Confirmed identification of Buspirone HCl using a Perkin Elmer 567 Grating Infared Spectrophotometer with NaCl match cell and $CHCl_3$ in the reference cell.

Determination of the Polymorph form of Buspirone HCl

(D)

wt of Container + Std (lot 18)	9.8219 gm
wt of Container	9.7810 gm
wt of Std from lot 18	0.0409 gm

(E)

wt of Container + Ref Std	9.9392 gm
wt of Container	9.7801 gm
wt of Ref Std	0.1591 gm

weighed on Perkin Elmer Autobalance AD-2Z
wt of Reference pan 10.680 mg

Thermal Analyst on Perkin Elmer DSC-2 -model 56 recorder. Init. Temp - 423°K Scan Rate - 10°/min
Range 20 mcal/sec Recorder input 10 MV Chart speed 20 mm/min

GENERAL CONTINUATION SHEET | PRODUCT Buspar Tablets | SAMPLE NO. 47926

Determination of the Polymorphic form of Buspirone - HCl

The sample Buspirone HCl MJ9022-1
MHJM266 I.G. - EXP 10/83 was found
Pass the specification as it shows
no peaks for B polymorph

Calc. checked
7-15-82
RJG

ANALYST(S) Robert E. Sutton | ANALYST NO. 875 | PAGE 2 OF ____ PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

7/1/82

weighed on Perkin Elmer Autobalance AD-2Z

Mixed Std No	wt of Std (c)
1	10.781 mg
2	10.296 mg
3	10.077 mg
4	10.160 mg
5	10.209 mg
6	10.971 mg

Reference Std MJ90221.4MJH266 Exp 10/83
weighed on Perkin Elmer autobalance AD2Z
wt #1 10.777 mg
#2 10.048 mg

wt of Photocopied Peaks	wt on PE AD-2Z
#1 0.0109 gm	10.85 mg
2 0.0097 gm	9.69 mg
3 0.0067 gm	6.74 mg
#4	7.38 mg
5	14.64 mg
6	9.81 mg

No peak of B polymorph were found in the samples of reference standard.

(1) $F = \frac{10.85\,mg}{(10.781\,mg)\frac{(40.9)\,mg}{(200.0\,mg)}} = 4.92$

2(F) $= \frac{9.69}{(10.296)(.204)} = 4.61$

3F) $= \frac{6.74}{(10.077)(.204)} = .328$

4F) $= \frac{7.38}{(10.160)(.204)} = 3.56$

5(F) $= \frac{14.64}{(10.209)(.204)} = 7.03$

6(F) $= \frac{9.81\,mg}{(10.971\,mg)(.204)} = 4.38$

ave (F) 4.63 mg peak wt/mg B

ATTACHMENT TO NDA 18-731 (IND 8705)
METHODS VALIDATION REQUEST AND REPORTING RECORD

SUMMARY OF RESULTS

A. Drug Substance: Buspirone HCL
Batch #3MAC233

Analyst

1. Assay: (pp. 244-249, 2066m)
100.6 %
99.2 %
Ave (2) = 99.9 %
NDA limits :
Dalia Stoup 8/18/82

2. TLC Identification: (pp. 235-236, 2042d)
One major spot matches the Rf of the Buspirone HCl standard (Rf = 0.51)
Walter E. Dunbar 8/19/82

3. Impurity MJ12687-1 by GC: (pp. 238-242, 2043j)
0.0% in Raw Material
0.0%
Avg (2) = 0.0%
NDA limit:
Walter E. Dunbar 8/19/82

4. Impurity MJ14660-1 by LC: (pp. 1204-1214, 2414b)
None detected
Dalia Stoup 8/18/82
NDA limits: maximum

5. Chloride by Titration: (pp. 225-227, 428dg)
8.42%
8.43%
Avg (2) = 8.42%
Walter E. Dunbar 8/19/82

6. Polymorph by DSC: (pp. 259-261, 2416a)
None of polymorph form B was Detected Sample Passes.
Robert E. Sutton 8/18/82

B. Dosage Forms: Buspirone Tablets
Batch #3MBM230 = 5 mg tablets
Batch #3MBC064 - 10 mg tablets

1. Assay (pp. 581-587, 2585g):
(pp. 625-630, 2585h)

5 mg
5.05 mg/tab (101.0%)
4.98 mg/tab (99.6%)
Ave (2) = 5.02 mg/tab 100.4%

10 mg
9.49 mg/tab (94.9%)
9.46 mg/tab (94.6%)
Ave (2) = 9.48 mg/tab 94.8%

limits: theoretical: 85-115%

Dalia Stonyo 8/18/82

2. Dissolution:
(pp. 588-591, 4050bd)
(pp. 632-635, 4050be)

The Dissolution of both 5 mg and 10 mg tablets complies with the USP specification.

Six, 5 mg tablets - range 95.8% - 100.7%, ave. 98.5%.
Six, 10 mg tablets - range 92.4% - 96.0%, ave. 93.6%.

Jellowitsall-Jr. DJB 8-17-82

3. Identification by IR:
(pp. 593-594, 4792a)
(pp. 637-638, 4792b)

The I.R. spectrum of both the 5 mg and 10 mg tablets match the Reference standard spectrum.

Robert E Sutton
8/19/82

GENERAL CONTINUATION SHEET	PRODUCT Buspar Tablets	SAMPLE NO. NDA 18-731

Dissolution : At 30 minutes

5 mg Tablet. Batch 3MBM230

	% Dissolution
Tablet # 1	95.8 %
2	97.4 %
3	99.6 %
4	99.9 %
5	97.7 %
6	100.1 %
AVG	98.5 %
SD	1.9 %
CV	1.9 %

NDA Limit : Each tablet must be greater than

10 mg Tablet - Batch 3MBC064

	% Dissolution
Tablet # 1	92.4 %
2	93.4 %
3	94.3 %
4	96.0 %
5	93.0 %
6	92.4 %
AVG	93.6 %
SD	1.4 %
CV	1.5 %

NDA Limit : Each tablet must be greater than

ANALYST(S) Ernest D. Brown	ANALYST NO.	PAGE 1 OF 5 PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

scale check 4/7/8: MTH

NDA 17-731
6-29-82
DJB

DISSOLUTION:

Automated System Linearity and Precision – 5mg system

Wyeth Buspirone Drug Substance: Lot 3MA-C233
DOE Electrobalance

10.165 mg ——→ 100.0ml 0.01N HCl STOCK

Linearity
3.0ml stock ——→ 100.0ml = 0.01N HCl
7.0ml " ——→ "
6.0ml " ——→ 50.0ml " (eq. to 12.0ml → 100.0ml)

Peaks tracked using a PDP-8E minicomputer

```
9999999
DJB
 9
 0.057 BASELINE
 0.175 - "  = .118
 0.174 - "  = .117   .117 AVG  3.0/100.0ml stock dilution
 0.176 - "  = .119
 0.326 - "  = .269
 0.326 - "  = .269   .269 AVG  7.0/100.0ml  "   "
 0.326 - "  = .269
 0.519 - "  = .462
 0.518 - "  = .461   .461 AVG  12.0/100.0ml  "   "
 0.518 - "  = .461
```

See linearity curve attached. System is linear thru 0.

Precision
10 injs of the 10.0ml ——→ 100.0ml stock dilution
PDP-8E tracking and calculations (STOVIF.BIN)

```
 0.267  0.267  0.267  0.266  0.267  0.268  0.268  0.269  0.269  0.268

MEAN:   0.2676 STD DEV:   0.0009661        COV:   0.361023
HIGH:   0.269  LOW:    0.266  RANGE:   0.00300002
```

System COV is 0.36%

NDA 18-731

6-30-82

USP Prednisone Dissolution Calibrator : Lot I=

50 RPM
Water, Vacuum deaerated, 37°C
Paddle

Std USP Ref Prednisone. Lot I-1
Pan = AD-22 Balance

1.482 mg —40 ml MeOH→ 100.0 ml = H_2O

30 ml of sample removed at 30 minutes and filtered thru Millipore AA (0.8 µm) filter, discarding first 5 ml.
Singlicates diluted 20.0 ml → 50.0 ml = H_2O

Tablet #1 $\frac{0.638}{0.652} \times \frac{1.482\ mg}{100.0\ ml} \times 900\ ml \times \frac{50.0\ ml}{20.0\ ml} \times \frac{100}{50\ mg}$ = 65.3 %

Tablet #2 0619 × 102.285 = 63.3 %

Tablet #3 0.638 × " = 65.3 %

Tablet #4 0660 × " = 67.5 %

Tablet #5 0.645 × " = 66.0 %

Tablet #6 0.642 × " = 65.7 %

AVE = 65.5 %
S.D. = 1.36 %
CV = 2.1 %

USP Limits -

Note: Since we don't have the 8 micron type SC Millipore filters we used the Millipore Type AA (0.8 microns).

NDA 18-731

7-1-82

Dissolution on 5 mg Tablets pp. 588-591
Batch 3MBM230

Response Ref. Std Batch MMJM266
PDE Electrobalance

9.985 mg → 100.0 ml @ 0.01 N HCl

10.0 ml → 100.0 ml 0.01 N HCl

Note: The series of 3 standard solutions was not used since the precision and linearity of the system is quite adequate for a single standard assay.

PDP-8E minicomputer tracking used.

Ave (2) Std response : $\frac{.373 + .373}{2} = .373$

Tab 1	response	.358
" 2	"	.364
" 3	"	.372
" 4	"	.373
" 5	"	.365
" 6	"	.376

Tab 1 % dissolution : $\frac{.358}{.373} \times \frac{9.985\,mg}{100.0\,ml} \times \frac{10.0\,ml}{100.0\,ml} \times 500\,ml \times \frac{100}{5\,mg} = 95.8\%$

$= .364 \times 267.69 = 97.4\%$

$= .372 \times$ " $= 99.6\%$

$= .373 \times$ " $= 99.9\%$

$= .365 \times$ " $= 97.7\%$

$= .376 \times$ " $= 100.7\%$

Ave = 98.5%
SD 1.9%
CV 1.9%

NDA LIMIT : EACH TABLET >
525 A.560 + P.1081

VOA 18-731
7-2-82
0.13

Dissolution:

Automated System Linearity and Precision - 10 mg System

Weight Equivalent Drug Substance : Lot 3MAC233

9.925 mg ⟶ 100.0 ml 0.01 NHCl STOCK

LINEARITY

6.0 ml stock ⟶ 100.0 ml = 0.01 NHCl
15.0 ml " ⟶ " "
6.0 ml " ⟶ 25.0 ml " (Eq. to 24.0 ml ⟶ 100.0 ml)

Plates tracked using a PDP-8E minicomputer

9999999
DJF
9
0.05 BASELINE
0.186 - " = .136
0.187 - " = .137
0.187 - " = .137
} .137 AVG 6.0 ml/100.0 ml STOCK DILUTION

0.39 - " = .340
0.386 " = .336
0.383 - " = .333
} .336 AVG 15.0 ml/100.0 ml " "

0.587 - " = .537
0.589 - " = .539
0.594 - " = .544
} .540 AVG 24.0 ml/100.0 ml " " (6.0 ml ⟶ 25.0 ml)

See linearity curve attached. System is linear thru 0

PRECISION

10 cups of the 15.0 ml ⟶ 100.0 ml stock dilution
PDP-8E tracking and calculations (STAFF 8A)

0.339 0.338 0.337 0.343 0.342 0.342 0.344 0.343 0.343 0.34

MEAN: 0.3411 STD DEV: 0.00242442 COV: 0.710766
HIGH: 0.344 LOW: 0.337 RANGE: 0.00699997

NDA 18-731
7-2-82
DJB

Dissolution:

Automated System Linearity and Precision - 10 mg System

Wyeth Bisphosphonate Drug Substance : Lot 3MAC233
DE Clathrostabrate

9.925 mg ⟶ 100.0 ml 0.01 N HCl : STOCK

LINEARITY
6.0 ml stock ⟶ 100.0 ml ∈ 0.01 "
15.0 ml " ⟶ " "
6.0 ml " ⟶ 25.0 ml " (Eq. to 24.0 ml ⟶ 100.0 ml)

Peaks tracked using a PDP-8E minicomputer

```
9999999
DJB
 9
 0.05 BASELINE
 0.186 - "   = .136 }
 0.187 - "   = .137 }  .137 AVE  6.0 ml/100.0 ml STOCK DILUTION
 0.187 - "   = .137 }
 0.39  - "   = .340 }
 0.386 - "   = .336 }  .336 AVE  15.0 ml/100.0 ml  "   "
 0.383 - "   = .333 }
 0.587 - "   = .537 }
 0.589 - "   = .539 }  .540 AVE  24.0 ml/100.0 ml  "   "   (6.0 ml → 25.0 ml)
 0.594 - "   = .544 }
```

See linearity curve attached. System is linear thru 0

PRECISION
10 reps of the 15.0 ml ⟶ 100.0 ml stock dilution
PDP-8E tracking and calculations (STAFF DA)

```
0.339  0.338  0.337  0.343  0.342  0.342  0.344  0.343  0.343  0.34

MEAN:  0.3411  STD DEV:  0.00242442        COV:  0.710766
HIGH:  0.344   LOW:  0.337   RANGE:  0.00699997
```

NDA 18-731

7-2-82

Dissolution on 10 mg Tablets pp. 632-635
Batch 3HBC064

Buspirone Ref Std Batch HMJM266
D&E Electrobalance

10.300 mg ⟶ 100.0 ml ≅ 0.01 N HCl

20.0 ml ⟶ 100.0 ml ≅ 0.01 N HCl

Note: The series of 3 standard solutions was not used since the precision and linearity of the system is quite adequate for a single standard assay.

PDP-8E minicomputer Keeping used

Ave(2) Std response = $\frac{.471 + .477}{2}$ = .474

Tab 1	response	= .425
" 2	"	.430
" 3	"	.434
" 4	"	.442
" 5	"	.428
" 6	"	.425

Tab 1 % dissolution = $\frac{.425}{.474} \times \frac{10.300\,mg}{100.0\,ml} \times \frac{20.0\,ml}{100.0\,ml} \times 500\,ml \times \frac{100}{10\,mg}$ = 92.4%

= .430 × 217.30 = 93.4%

= .434 × " = 94.3%

= .442 × " = 96.0%

= .428 × " = 93.0%

= .425 × " = 92.4%

AVE 93.6%
SD 1.4%
CV 1.5% ✓

NDA Limit: Each Tablet
See p. 1085

GENERAL CONTINUATION SHEET	PRODUCT Buspar Tablets	SAMPLE NO. NDA 18-731

Drug Substance Batch # 3MAC233

Assay for Buspirone HCl (pp 244-249, 2066m)

Found 100.6 %
99.2 %
Ave (2) = 99.9 %

Determination of chlorobuspirone impurity MJ14660-1 by LC (pp 1204-1214, 2414b)

Results: none detected. NDA limits

Dosage Forms 5mg & 10mg

Assay (pp. 581-587, 2585g
pp. 625-630, 2585h)

NDA specs:

5mg

Results: 5.05 mg/tab (101.0%)
4.98 mg/tab (99.6%)
Ave (2): 5.02 mg/tab 100.4%

10mg

9.49 mg/tab (94.9%)
9.46 mg/tab (94.6%)
Ave (2): 9.48 mg/tab (94.8%)

ANALYST(S) Dalia Stoup	ANALYST NO. 564	PAGE 1 OF 8 PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Def II

NDA #18-731
P-3

	STD PEAK AREA / I.S. PEAK AREA	R
③	10900000 / 5466800	1.994
④	10779000 / 5413300	1.991
⑤	10790000 / 5440800	1.983
⑥	10910000 / 5443600	2.004
		Avg 1.993

	SPL PEAK AREA / I.S PEAK AREA	R
①	10868000 / 5471300	1.986
②	10790000 / 5440800	1.983
		Avg: 1984

$$\%\ \text{buspirone HCl} = \frac{1.984}{1.993} \times \frac{100.2\text{mg}}{200\text{ml}} \times \frac{10.0\text{ml}}{50\text{ml}} \times \frac{200\text{ml}}{100.6\text{mg}} \times \frac{50\text{ml}}{10.0\text{ml}} \times 100$$

$$= 99.2$$

Avg of 2 determinations: 99.9 %

HPLC System

Pump: Perkin Elmer Series 2
Column: μ Bondapak (Waters) 30cm x 3.9mm I.D.
Injector: Micromeritics 725 Autoinjector equipped with 20μl loop
Detector: Du Pont uv Spectrophotometer set at 254 nm
Mobile Solvent: 475ml of CH_3CN + 600ml buffer; Flow: 2 ml/min
Integrator: 3390A Hewlett Packard Integrator
(see chromatograms for conditions)

Determination of Buspirone HCl in Buspar 5mg Tablets

Method: 2585g

HPLC conditions - same as for drug substance

Internal Std & buspirone HCl std solutions prepa-rations shown on back of p.1

Sample preparation:

10 tablets → 100ml
25ml in ml
q.s H2O

10.0ml + 10.0ml I.S. → 50.0ml

Determination I

	STD PEAK AREA / I.S. PEAK AREA	R
⑤	10790000 / 5440800	1.983
⑥	10910000 / 5443600	2.004
⑦	10868000 / 5477900	1.984
⑧	10832000 / 5463900	1.982
		Avg: 1.988

	SPL PEAK AREA / I.S. PEAK AREA	R
①	10888000 / 5456100	1.996
②	10949000 / 5441100	2.012
		Avg: 2.004

$$\frac{\text{mg buspirone HCl}}{\text{tablet}} = \frac{2.004}{1.988} \times \frac{100.2\text{mg}}{200\text{mg}} \times \frac{10.0\text{ml}}{50.0\text{ml}} \times \frac{100\text{ml}}{10\text{tabs}} \times \frac{50\text{ml}}{10.0\text{ml}}$$

DS

$$= 5.05 \quad \text{Decl: } 5\text{mg} \quad 101.0\%$$

Determination II

STANDARDS - same as in determination I

	SPL PEAK AREA / I.S. PEAK AREA	R
①	10829000 / 5491500	1.972
②	10831000 / 5472500	1.979
		Ave: 1.976

NDA # 18-731

$$\frac{\text{mg buspirone HCl}}{\text{tablet}} = \frac{1.976}{1.988} \times \frac{100.2\text{ mg}}{200\text{ ml}} \times \frac{10.0\text{ ml}}{50\text{ ml}} \times \frac{100\text{ ml}}{10\text{ tabs}} \times \frac{50\text{ ml}}{10.0\text{ ml}} \quad p.5$$

$= 4.98$ 99.6%

Avg of two determinations : 5.02 mg/tab 100.4 %

NDA limits : Theoretical –
(p. B560) Minimum –
Maximum –

Determination of Buspirone HCl in Buspar #10 mg Tablets

Method : 2585h
HPLC conditions - same as for drug substance
Internal Std + buspirone HCl Std solution preparations shown on back of p.1

Sample preparation

10 tablets → 200 ml
50 ml of 1N HCl
q.s. H2O

10.0 ml
+ 10.0 ml I.S. → 50 ml

Determination I

	STD PEAK AREA / I.S. PEAK AREA	R
(7)	10868000 / 5477900	1.984
(8)	10832000 / 5463900	1.982
(9)	10922000 / 5495100	1.988
(10)	10876000 / 5476300	1.986
		Avg : 1.985

	SPL PEAK AREA / I.S. PEAK AREA	R
(1)	10317000 / 5485500	1.881
(2)	10306000 / 5484100	1.879
		1.880

$$\frac{\text{mg buspirone HCl}}{\text{tablet}} = \frac{1.880}{1.985} \times \frac{100.2\text{ mg}}{200\text{ ml}} \times \frac{10.0\text{ ml}}{50.0\text{ ml}} \times \frac{200\text{ ml}}{10\text{ tabs}} \times \frac{50\text{ ml}}{10.0\text{ ml}}$$

$= 9.49$ Decl : 10 mg/tab 94.9 % of decl

Determination II

STANDARDS - same as in Det I

	SPL PEAK AREA / I.S. PEAK AREA	R
①	10241000 / 5521500	1.855
②	10284000 / 5436100	1.892
		1.874

$$\frac{\text{mg buspirone HCl}}{\text{tablet}} = \frac{1.874}{1.985} \times \frac{100.2\text{mg}}{200\text{ml}} \times \frac{10.0\text{ml}}{50\text{ml}} \times \frac{200\text{ml}}{10\text{tabs}} \times \frac{50\text{ml}}{10.0\text{ml}}$$

$= 9.46$ Decl: 10 mg/tab 94.6 % of decl

$$\text{Avg of 2 det} = \frac{9.49\text{mg/tab} + 9.46\text{mg/tab}}{2}$$

$= 9.48$ (94.8 % of decl)

NDA limits: Theoretical –
Minimum –
(p B 604) Maximum – 1

Determination of Chlorobuspirone in Buspirone Hydrochloride Raw Material (MJ14660-1)

Method: 24/4b

Standard Solution

Buspirone HCl
MMJ1266

G: 10.3555 gm
T: 10.2153 "
N: 0.1002 gm → 100 ml (H2O)
+5.0 ml
MJ14660-1

MJ14660-1 Stock Solution (1)
(Perkin Elmer HD-27 Autobalance)

G: 5.196 mg
T: 0.009 "
N: 5.187 mg → 50 ml (H2O)

Diluted MJ14660-1 Solution (2)

5.00 ml → 100 ml (H2O)

Sample Preparation
Buspirone Drug Subst 3MAC233

G: 10.4880 gm
T: 10.3876 "
N: 0.1004 gm → 100 ml
5.0 ml MJ14600-1 Sol. 1

SYSTEM PRECISION TEST performed on MJ14660-1 Solution (2)

Peak areas
(1) 60437
(2) 61365
(3) 64104
(4) 61871
(5) 62670
(6) 62805 Ave: 62209 S=1275 2.05%

% RSD is good on 4 consecutive buspirone std + MJ14600-1 injections, but two injections made after drug subst injections seems to fall off.

HPLC System
Pump: Perkin Elmer Series 2
Injector: WISP 710B Autoinjector 202
Detector: Perkin Elmer LC-75 set at
Mobile Solvent: 475 ml CH_3CN + 600 ml 1% HAc
Integrator: Waters Data Module Model 730 operating conditions printed on chromatograms

printed on chromatograms)

No chlorobuspirone detected in duplicate sample injections.

calculations checked
7-22-92
R. Ballbach

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Memorandum

Date November 13, 198

From Chief, Drug Standards Research Branch, HFN-420

Subject Methods Validation for NDA 18-731, Buspar (buspirone) Tablets

To Francis A. Zinsitz, HFN-120

The results of our laboratory investigations of the subject NDA show that the proposed methods will be suitable for regulatory and control purposes once some minor questions are addressed.

1. HPLC Assays:
a. If the column has to be rinsed at the end of each day with 90 ml of water and 90 ml of acetonitrile:water (90:10)? The method should explicity state this fact. Our column was prewashed as above but washed overnight with water. The resolution between the internal standard and buspirone HCl decreased each day.
b.The method requires filtration of the tablet solutions through 515 fast fluted paper. The supplier, Eaton-Dikeman should be specified if only this particular paper is suitable or the use of an equivalent permitted. Elsewhere in the submission the effect of various filter papers was reported in regard to a UV assay. Based on this report the firm recommends Whatman #1 with the first 20 ml discarded.

2. Dissolution: DDC utilized a manual adaptation of the automated procedure in the proposed methods. The firm should be requested to add instructions for manual use.

3. IR- Identification: The thickness of the IR liquid cell is not specified in the Tablet ID test.

4. Chlorobuspirone: An additional parameter, e.g. resolution, is required for the system suitability test. At present only the relative standard deviation is specified.

5. MJ 12687-1: An additional parameter, e.g. rsolution, is required for the system suitability test. At present only the relative standard deviation is specified.

6. Other Impurities: We did not receive any of the other known potential impurities. Thus, we can only assume that these compounds are quantifiable under the conditions proposed by the firm. This is especially critical for the dosage form since no methods are included for this purpose. We suggest a combination of GC and TLC.

Our results are presented below:

NDS Lot 3MAC 233

Procedure	Limits	DET	DDC
Assay-HPLC (%)		99.9	100.6
Identification-TLC		passes	passes
Impurity MJ 12687-1-GC (%)		none	none
Impurity MJ 14660-1-LC (%)		none	none
Chloride (%)		8.42	8.38
Residual Solvents-GC (%) tot ea		-	0.1
Polymorph B-DSC		none	none

Dosage Form 5 mg Tablets Lot 3MBM230

Assay-HPLC (%)	90-110	100.4	100.2
Dissolution (%)			
average		98.5	105.2
range			
Identification-IR		passes	passes

Dosage Form 10 mg Tablets Lot 3MBC064

Assay-HPLC (%)	90-110	94.8	95.2
Dissolution (%)			
average	nlt	93.6	96.3
range			
Identification-IR			

No major difficulties were encountered.

Eric B. Sheinin

Eric B. Sheinin, Ph.D.

Attachments

FLAG

ANALYST WORKSHEET

1. PRODUCT: Buspar (buspirone) tablets

2. SAMPLE NUMBER: NDA 18-731

3. SEALS: ☐ INTACT ☒ NONE ☐ BROKEN

4. DATE REC'D: 5-27-82

5. RECEIVED FROM: E. Shemin

6. DISTRICT OR LABORATORY: HFD-420

7. DESCRIPTION OF SAMPLE

8. NET CONTENTS: ☐ NOT APPLICABLE ☐ NOT DETERMINED ___ UNITS EXAMINED
DECLARE/UNIT ____ AMOUNT FOUND ____ % OF DECLARED ____

9. LABELING: ____ ORIGINAL(S) SUBMITTED ____ COPIES SUBMITTED ☐ NONE

10. SUMMARY OF ANALYSIS

NDS not 3MAC 233

Assay: 99.4 %

100.1

101.1

101.9

Ave 100.6 %

Limits:

TLC - NDS has same Rf as ref std buspirone HCl.

Chloride - found: 8.38 %
8.38 % > 8.38 %

Limits:

11. RESERVE SAMPLE

12. a. ANALYST SIGNATURE (Broke Seal ☐) Brent D. Cummings

b.

c.

13. WORK-SHEET CHECK

a. BY: Eva B. Klein

b. DATE: 7/8/82

14. DATE REPORTED: 6-15-82

18-731

Received:

5 mg/tab - Batch # 3MBM230
10 mg/tab " # 3MBC064
NDS " # 3MAC233
buspirone ref std " # MMJM266

Propylparaben MMAE-272

Sup. MJ4660-1 #1
Sup. MJ12687-1 #1
Octanesene LHC-045

Low melting polymorph of MJ9022-1 # 3MDN162

NMS - Assay by HPLC

wt. of Propylparaben (int. std.)

.4090 g
.3439 g
.0651 g / 25 ml MeOH / 500 ml H_2O /

wt of Ref. std.

(1)
36.25656
36.23174 g
.02482 g / 50 ml

(2)
36.08990
36.06264 g
.02726 g / 50 ml

(12.5 ml 1N HCl - to volume with H_2O)

NDS

(1)
37.19495
37.16885 g
.02610 g / 50 ml

(2)
35.53394
35.50722 g
.02672 g / 50 ml

(12.5 ml 1N HCl - to volume with H_2O)

In assay each was treated as follows:

10.0 ml of Ref or NDS + 10.0 ml int. std → 50 ml H_2O

Acidified with Nitric Millipore LS (5u) Li Kar

GENERAL CONTINUATION SHEET	PRODUCT Bespar	SAMPLE NO. NDA 18-731

Impurity chromatography - MJ 14660-1

- none found

Impurity - 1,4-Di (2-pyridyl dithio) piperazine dihydrochloride or MJ 12657-1

- none found

Residual solvents:

ether - none found

iPrOH - 0.1%

Smith:

DSC - 200°C - NDS melted around 207°

Ref std - 206°

low melting polymorph std ~150°

- no low melting polymorph detected in NDS.

ANALYST(S) Donald G. Cummings Green	ANALYST NO.	PAGE 2 OF 16 PAGES

μ Bondapak C18 30 cm x 3.9 mm 25°

254nm at .8 AUFS

CH_3CN - .01M KH_2PO_4 pH 7.5 (40-80) 2 mL/min

sample size 25 μl

Resolution:

$$R = \frac{2(t_2 - t_1)}{w_1 + w_2} = \frac{2(215 - 74)}{7+24} = 5.77$$

Results:

	Ret. Std. (Ret. time 234sec = 3.9 min)	Bupion- (643sec = 10.7 min)	Ratio B/INT. STD.	
Ref. 1	133463	243621	1.825	
	132210	237412	1.796	1.806
	138032	244413	1.771	
	132952	240995	1.813	
	131753	239355	1.817	
	129194	234717	1.817	
NDS 1	130354	241462	1.848	
	131565	252279	1.917	1.888
	136199	251936	1.850	
NDS 2	129653	253922	1.997	
	133790	260988	1.951	1.966
	132132	257557	1.949	
Ref. 2	130671	259141	1.983	1.969
	133394	260822	1.955	

GENERAL CONTINUATION SHEET	PRODUCT Buspar	SAMPLE NO. NDA 18-731

Tablets:

Dissolution - R. panicker to inj. std buspirone HCl. for both dosage forms.

Dissolution:

5mg/tab tablets Lot # 3MBM230

	vs inj std. (single point)		from std curve	
High	5.50 mg	110.0%	5.45 mg	109.0%
Low	5.13 mg	102.6%	5.10 mg	102.0%
Ave (6)	5.26 mg	105.2%	5.22 mg	104.4%

10mg/tab tablets Lot 3MBC060

High	9.74 mg	97.4%	9.75 mg	97.5%
Low	9.48 mg	94.8%	9.45 mg	94.5%
Ave (5)	9.63 mg	96.3%	9.60 mg	96.0%

Limits:

Assay:

5mg/tab:	4.97 mg	99.4%
	4.95	99.0%
	5.07	101.4%
	5.05	101.0%
Ave	5.01 mg	100.2%

Limits:

ANALYST(S) Daniel D. Cummings	ANALYST NO.	PAGE 3 OF 16 PAGES

p 3

NDA 18-731

vs Ref 1

1) $\frac{1.888}{1.806} \times 24.82 \times \frac{100}{26.10} = 99.4$

2) $\frac{1.966}{1.806} \times 24.82 \times \frac{100}{26.72} = 101.1$

vs Ref. 2

$\frac{1.888}{1.969} \times 27.26 \times \frac{100}{26.10} = 100.1$

$\frac{1.966}{1.969} \times 27.26 \times \frac{100}{26.72} = 101.9$

Ave 100.6 %

Limits:

TLC

Silica Gel 60 F254nm (Merck) 250u, activated 20min 105° C

$CHCl_3$ - EtOH (88-12) (saturated tank)

Plant UV

Ref std 30mg / 3ml $CHCl_3$ 20 x (200ug) spotted

↓ 10 x (100ug)

1 → 10ml $CHCl_3$ 1 x (1ug)
2 x (2ug)
5 x (5ug)

NDS 30mg / 3ml $CHCl_3$
20 x (200ug)
10 x (100ug)

NDS - Ref std have same Rf $\frac{7.4}{15} = .49$

no additional spots noted.

GENERAL CONTINUATION SHEET	PRODUCT Buspar	SAMPLE NO. NDA 18-731

10mg / Tab.	9.50 mg	95.0%
	9.34	93.4%
	9.70	97.0%
	9.53	95.3%
Av.	9.52 mg	95.2%

Lauds:

HPLC - assay in NDS and tablets

Resolution - if retention time and peak width are measured in mm or cm, division of peak width by by chart speed is not necessary.

Does a column have to be rinsed at the end of each day with 90 ml of water and 90 ml of CH_3CN-H_2O (90-10)? If it is necessary to do so, it should be specified. [Before starting the assay column was pumped as above, but then it stood from one day to the next it was washed

ANALYST(S) Renate G. Cunningham	ANALYST NO.	PAGE 4 OF 16 PAGES

NDA 18-723

HPLC -

Linearity

Ref. 1 used

1) 2.0 ref stock + 5.0 ml INT STD. → 25 ml H2O (.0397 mg/ml)
2) 4.0 " + 5.0 " → 25 " (.0794 mg/ml)
3) 5.0 " + 5.0 " → 25 " (.0993 mg/ml)
4) 6.0 " + 5.0 " → 25 " (.1191 mg/ml)

Conc.	INT. STD.	BL/STD.	Ratio BL/INT. STD.	
Lin. #4	131567 ✓	279269 ✓	2.123 ✓	2.163 ✓
	127257 ✓	277336 ✓	2.179 ✓	
	127037 ✓	277737 ✓	2.186 ✓	
Lin. #3	132513 ✓	240925 ✓	1.818 ✓	1.807 ✓
	126047 ✓	227937 ✓	1.802 ✓	
	126642 ✓	228788 ✓	1.807 ✓	
Lin #2	131152 ✓	187685 ✓	1.431 ✓	1.453 ✓
	125829 ✓	183670 ✓	1.459 ✓	
	126666 ✓	186134 ✓	1.469 ✓	
Lin #1	131195 ✓	99568 ✓	.759 ✓	.750 ✓
	125898 ✓	95180 ✓	.756 ✓	
	129351 ✓	95090 ✓	.735 ✓	

Linearity through points tested.

GENERAL CONTINUATION SHEET	PRODUCT Bloxpan	SAMPLE NO. NDA 18-731

overnight with water. Dissolution between internal standard and bisoprolol HA decreased each day, first day giving resolution of 8.8, 2nd day - 4.7 and third day 4.0].

Expected retention times for internal standard and bisoprolol should be specified in the method, and mobile phase may be changed to obtain desired retention times.

Tablet grinding are to be filtered through 515 filter. If desired to specified it is Celite - Dikaman filter 515 filter. Is it necessary to use that particular paper or may its equivalent be used?

Dissolution - manual method in addition to autosampler are desired to include:

ANALYST(S) Annette G. Cunningham	ANALYST NO.	PAGE 5 OF 16 PAGES

FD FORM 431c (3-71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

18-731

Chloride

wt of NDS

① 64.6909 / 64.2894 g = .4015 g

② 67.6597 / 67.2364 g = .4233 g

20.0 ml 0.10333 N $AgNO_3$ used

0.10764 N NH_4SCN needed

① 10.38 ml ② 9.90 ml

calc. % Cl = $\left(\text{ml } AgNO_3 \times N - \text{ml } NH_4SCN \times N\right) \times \frac{35.45}{\text{wt of sample (mg)}} \times 100$

1) $\left(20.0 \times .10333 - 10.38 \times .10764\right) \times \frac{35.45}{401.5} \times 100 = 8.38\%$

2) $\left(20.0 \times .10333 - 9.90 \times .10764\right) \times \frac{35.45}{423.3} \times 100 = 8.38\%$

limits

18-731

Chloride

wt of NDS

①	②
64.6909	67.6597
64.2894 g	67.2364 g
.4015 g	.4233 g

20.0 ml 0.10333 N $AgNO_3$ used

0.10764 N NH_4SCN needed

①	②
10.38 ml	9.90 ml

calc. % Cl = $\left(\text{ml } AgNO_3 \times N - \text{ml } NH_4SCN \times N\right) \times \frac{35.45}{\text{wt of sample (mg)}} \times 100$

1) $\left(20.0 \times .10333 - 10.38 \times .10764\right) \times \frac{35.45}{401.5} \times 100 = 8.38\%$ ✓

2) $\left(20.0 \times .10333 - 9.90 \times .10764\right) \times \frac{35.45}{423.3} \times 100 = 8.38\%$ ✓

limits

GENERAL CONTINUATION SHEET | PRODUCT Buspar | SAMPLE NO. NDA 18-731

Tablet identification by IR - thickness of IR cell is not specified.

Chromatography - no system suitability such as required resolution between buspirone and chromatographic change in mobile phase composition to obtain baseline resolution were included in the method.

Impurities and degradation products - HPLC

The proposed HPLC system does not separate compounds II, V and VI or not separated from each other or impurity III from compound VIII. If impurity were to be detected - present - in Buspirone HCl it would be impossible from the chromatogram to say which impurity it may be if it eluted at the

ANALYST(S) Daniel B. Cunningham | ANALYST NO. | PAGE 6 OF 16 PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

IMPURITY MJ 14660-1

Wt of imp.

.020990 g
.015555 g

.005435g / 50ml H_2O

NDS

(1) 34.9316 g
34.8774 g

.0542g / 50ml

(2) 34.7666 g
34.7166 g

.0500g / 50ml

Solvent: H_2O

Ref std

(1) 40.6941 g
40.6458 g

.0483g / 50ml

(2) 35.7007 g
35.6511 g

.0496 g
+ 2.0 ml imp
↓
50ml H_2O

(3) 38.7005 g
38.6504 g

.0501g
+ 4.0ml imp
↓
50ml H_2O

(4) 34.2310 g
34.1814 g

.0496 g
+ 5.0ml imp
↓
50ml H_2O

(5) 40.0000 g
39.9520 g

.0480g
+ 6.0 ml imp
↓
50ml H_2O

(.2174 mg/ml imp) (.4348 mg/ml imp) (.5435 mg/ml imp) (.6522 mg/ml imp)
(equiv. .420 / .840 (10-20) (1.3-2)

Bondapak C18 30cm x 3.9mm 25° 254nm

CH_3CN - 1% HOAc in 1:0 (35-65) 2ml/min

25ul injected ret. of imp ≈ 10.5 min.

	Area/imp.		
Ref 5	94147	93667	NDS - no impurity detected
	92212		
	94832		
Ref 4	70750	71960	
	71772		
	74023		
Ref 3	50684	50546	
	49415		
	51469		
	50610		
Ref 2	27285	25780	
	25155		
	24891		

GENERAL CONTINUATION SHEET	PRODUCT Buspar	SAMPLE NO. NDA 13-731

same time as above specified impurities.

TLC system used for identification of NDS from company's data appears to separate buspirone from possible impurities, except for compounds III, IV and V which have similar Rf.

Combination of GC and TLC would probably eliminate which impurity was present, except the suggested GC is not required confirmation for the analysis of NDS.

ANALYST(S) Dennis G. Williams	ANALYST NO.	PAGE 7 OF 16 PAGES

FD FORM 431a (3/71) REPLACES FORM FD 431-1 WHICH MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Suggested system by company was
CH_3CN - 1% HOAc (40-60) 2ml/min.
Required resolution between bisoprolol
and impurity C (bisoprolol impurity not
stated).

On column used Baselli verification was
not obtained by using suggested mobile phase
at the required rate. Baselli verification
may be obtained either by slowing down
the flow of mobile phase (to ~ 1,0ml/min)
or by changing composition of mobile
phase (ex. CH_3CN - 1% HOAc 35-65).

IMP. MJ 12687-1 p 8

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wt of octachrome INT std.

.3712 g
.3364 g

.0348 g / 100 ml

wt of MJ-12687-1

.020410 g
.015567 g

.004843 g / 50 ml CH_2Cl_2 (stock)

(.09686 mg/ml)

wt of NDs

(1)

72.0161
71.9088 g

107.3 g

INC Tridecane I.S. 7.0 ml
10.0 ml MeOH

↓
100 ml CH_2Cl_2

(2)

69.4710
69.3387 g

.1323 g

+ nonane I.S 7.0 ml I.S
10.0 ml MeOH

↓
100 ml CH_2Cl_2

Std. 10.0 ml std stock + 7.0 ml INC I.S. → 100 CH_2Cl_2

8.0 ml std stock + 7.0 ml I.S. → 100 ml CH_2Cl_2

4.0 ml std stock + 7.0 ml I.S. → 100 ml CH_2Cl_2

3% OV 17 on Gas Chrom Q (100/120 INC mesh)

6' x 2 mm

Col. T. 255°
INJ. T. 275°
FID 300°
H_2 60 ml/min

Col. Flow IMP. ~ 6% / min

octa squalane ~ 6.0 min

at Col T. 275° IMP. ~ 2.3 min, INT STD. 3.0 min (compared IMP. 2.1, INT. STD. 3.2 min)

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255° cor. T.

	IMP.	I.S.	Ratio IMP/IS	
Rf 10/100	2236 ✓	7468 ✓	.2994 ✓	
	2447 ✓	9208 ✓	.2657	
	2339 ✓	11060 ✓	.2567 ✓	Ave .2634 ✓
	2787 ✓	10840 ✓	.2571 ✓	
	3044 ✓	10410 ✓	.2924 ✓	
	2813 ✓	10510 ✓	.2676 ✓	
	3024 ✓	11200 ✓	.2700 ✓	
NDS-1	—	8936 ✓		
NDS-2	—	11090 ✓		
Rf 8/100	2485 ✓	11880 ✓	.2094 ✓	
	2624 ✓	12690 ✓	.2068 ✓ } } .2051 ✓	
	2402 ✓	12060 ✓	.1992 ✓ }	
Rf 4-7100	1243 ✓	11760 ✓	.1057 ✓ }	
	1362 ✓	13400 ✓	.1016 ✓ } } .1055 ✓	
	1358 ✓	12430 ✓	.1093 ✓ }	

at 275°

Rf 10→100	3075 ✓	11650 ✓	.2639 ✓	
	3159 ✓	11820 ✓	.2673 ✓	
	3186 ✓	11920 ✓	.2673 ✓	.2661 ✓
	3087 ✓	11460 ✓	.2694 ✓	
	3376 ✓	12850 ✓	.2627 ✓	
	2966 ✓	11140 ✓	.2662 ✓	
Rf 8→100	2567 ✓	11610 ✓	.2211 ✓	
	2162 ✓	10180 ✓	.2124 ✓ } .2185 ✓	
	2329 ✓	10490 ✓	.2220 ✓	
Rf 4→100	1313 ✓	10910 ✓	~~.1203~~ ✓	
	1336 ✓	12620 ✓	.1059 ✓	
	1320 ✓	12590 ✓	.1048 ✓ } .1067 ✓	
	1380 ✓	12630 ✓	.1093 ✓	
NDS-1	—	13430 ✓		
NDS-2	—	13410 ✓		

No impurity detected in NDS

Residual Solvents

wt of sample (NDS) (1)	(2)	wt of ether	wt of iPrOH
23.6130 g	23.5257 g	39.2781 g	39.6010 g
23.5123	23.4155	39.1805	39.4986
.1007 g / 10.0 ml	.1102 g / 10.0 ml	.0976 g / 10ml	.1024 g / 10ml

solvent N,N-dimethylacetamide (DMAC)

Stds mixture:

1.0ml ether extr 1.0ml iPrOH extr → 100ml (A)

(.0976 mg/ml ether + .1024 mg/ml iPrOH)

8.0 A → 10ml (B)

(.078 mg/ml ether + .0819 mg/ml iPrOH)

5.0 A → 10ml (C)

(.0488 mg/ml ether + .0512 mg/ml iPrOH)

28% Pennwalt 233 / 4% KOH on 80/100 Gas Chrom R

6' x 4mm

Temp. 1	100°
Time 1	6.0
Rate	8.0
Temp 2	180
Time 2	~~5~~ none
Inj.	200
FID	300

p. 11

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Grade	Value	Found
Std. A	23160 —	23120 ✓
Std B	20550 ✓	18670 ✓
Std C	11760 —	10670 ✓
NDS 1	—	2323 ✓
NDS 2	—	2541 ✓

No value declared in NDS

% Found ① $\frac{2323}{23120} \times \frac{102.4}{10} \times \frac{1}{100} \times 10 \times \frac{100}{100.7} = .1\%$

② $\frac{2541}{23120} \times \frac{102.4}{10} \times \frac{1}{100} \times 10 \times \frac{100}{110.2} = .1\%$ ✓

Mwi 6

DSC

DuPont 990

Ref std MMJM266 at ~206°

Ref std hot #1 ~ 188°

NDS ~ 207°, no low melting polymorph detected

— pass

Tablets

Identification - IR - Spectra submitted -
5 mg tab. extract = 10 mg tab. extract have
similar spectra to that of ref. std.

5 mg tabs - 40 tab. used ; 110 ml CH_2Cl_2
10 mg tabs - 20 " 110 ml CH_2Cl_2
200 mg ref std / 10 ml CH_2Cl_2

Dissolution

Wt'd Ref Std (note)
.02448 g
.01555 g

.0653 g / 50 ml .01N HCl

Dilutions
For 5 mg tabs

A) 3.0 ml stock → 100 ml (.00352 mg/ml) ✓
B) 7.0 ml " → 100 ml (.00821 mg/ml) ✓
C) 6.0 ml " → 50 ml (.01407 mg/ml) ✓

For 10 mg tabs

A) 6.0 ml stock → 100 ml (.00704 mg/ml) ✓
B) 15.0 " → 100 ml (.01759 mg/ml) ✓
C) 6.0 " → 25 ml (.02814 mg/ml) ✓

5 mg tabs - 6 tabs assayed 1 tab → 500 ml .01N HCl
10 mg tabs - 6 tabs assayed 1 tab → 500 ml .01N HCl

30 min.

Ti Nitrol through Millipore LS 5 μ filter

Dissolution cont'd P 13

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abs at 235nm

5 mg Tab

Ref. A .173 ✓
B .418 ✓
C .727 /

5mg #1	.500	$\times \frac{1}{.418}$ (Ref B) $\times$ .00821 $\times$ 500	= 5.50 mg	110.0% ✓ High
#2	.522 ✓	x 9.820	= 5.18 ✓	103.6% ✓
#3	.542 ✓	x 9.820	= 5.38 ✓	107.6% ✓
#4	.522 ✓	"	5.13 ✓	102.6% Low
#5	.530 ✓	"	5.20 ✓	104.0% ✓
#6	.524 ✓	"	5.15 ✓	103.0% ✓
		Ave	5.26 ✓	105.2% ✓

10mg / tab

Ref A .356 ✓
B .904 ✓
C 1.460

10mg #1	.478 ✓	$\times \frac{1}{.904}$ (= Ref B) $\times$ .01759 $\times$ 500	= 9.51 mg ✓	95.1% ✓
[?] #2	1.092 ✓	x 9.729	10.68 mg ✓	(106.8%) (?)
#3	.988 ✓	"	9.61 mg	96.1 ✓
#4	.974 ✓	"	9.48 mg Low	94.8 ✓
#5	1.004 ✓	"	9.77 mg	97.7 ✓
#6	1.006 ✓	"	9.79 mg High	97.9 ✓
		Ave	9.63 (w/out #1 & #2)	96.3% ✓

Dissolution Control p-14 18-731

Results using standard curve

5 mg/tablet

	mg/tab		%
1) .0109 × 500 =	5.45 mg	High	109 %
2) .0103 × 500 =	5.15 mg		103 %
3) .0107 × 500 =	5.35 mg		107 %
4) .0102 × 500 =	5.10 mg	Low	102 %
5) .0103 × 500 =	5.15 mg		103 %
6) .0102 × 500 =	5.10 mg		102 %
Ave	5.22 mg		104.4 %

10 mg/tablet

1) .0190 × 500 =	9.5 mg		95 %
[2) .0212 × 500 =	10.6 mg		106 %]
3) .0191 × 500 =	9.55 mg		95.5 %
4) .0189 × 500 =	9.45 mg	Low	94.5 %
5) .0195 × 500 =	9.75 mg	High	97.5 %
6) .0195 × 500 =	9.75 mg		97.5 %
Ave	9.6 mg/tab		96.0 %

(#2 not used)

Tablets - assay

5 mg tablets 10 tablets + 25 ml 1N HCl → 100 ml H_2O

10 mg tabs 10 " + 50 ml 1N HCl → 200 ml H_2O

Done in duplicate

Filtered thru S&S 588 filter (do not have ED 515)

Each treated as follows:
10.0 ml of appd solution + 10.0 ml int. std → 50 ml H_2O

Each solution filtered through Millipore LS
filter before assay.

For int. std. preparation and int std. curve
and preparation see W/S p. 1.

Curve	Int. std.	Response	Ratio R/int. std.	
Ref. 2	127969	245719	1.92	
	121712	241686	1.956	
	121419	241449	1.989	
5 mg tab. #1	134914	246365	1.826	
	130762	239403	1.831	1.832
	128044	235424	1.838	
5 mg tab. #2	135030	252972	1.873	
	135553	250030	1.844	
	130085	231395	1.779	1.823
	130100	233853	1.797	
Ref. #1	131135	231827	~~1.765~~	
	126753	235053	1.854	
	127374	231797	1.820	1.830
	128183	232910	1.817	
10 mg tab #1	128543	225371	1.753	
	129708	228860	1.764	1.752
	130054	226375	1.740	

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HPLC cont'd

	Area	Int. Std.	Response	Ratio R/int. std	
10mg tab #2	133424		228098	1.709	1.721
	129309		223191	1.726	
	129894		224594	1.729	
Rf 2	135126		267523	1.980	
	131609		260364	1.978	
	131024		257148	1.962	

Rf 2 Ave (6) = 1.969

5mg tabs

vs Ref #1

1) $\frac{1.832}{1.830} \times \frac{24.82}{50} \times 100 \times \frac{1}{10} = 4.97\,mg$ 99.4%

$\frac{1.832}{1.960} \times \frac{27.26}{50} \times 100 \times \frac{1}{10} = 5.07\,mg$ 101.4%

2) $\frac{1.823}{1.830} \times \frac{24.82}{50} \times 100 \times \frac{1}{10} = 4.95\,mg$ 99.0%

$\frac{1.823}{1.969} \times \frac{27.26}{50} \times 100 \times \frac{1}{10} = 5.05\,mg$ 101.0%

Ave 5.01 mg 100.2%

10mg tabs

1) $\frac{1.752}{1.830} \times \frac{24.82}{50} \times 200 \times \frac{1}{10} = 9.50\,mg$ 95.0%

$\frac{1.752}{1.969} \times \frac{27.26}{50} \times 200 \times \frac{1}{10} = 9.70\,mg$ 97.0%

2) $\frac{1.721}{1.830} \times \frac{24.82}{50} \times 200 \times \frac{1}{10} = 9.37\,mg$ 93.7%

$\frac{1.721}{1.969} \times \frac{27.26}{50} \times 200 \times \frac{1}{10} = 9.53\,mg$ 95.3%

Ave 9.52 mg 95.2%

NDA limits