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**BUSPAR<sup>®</sup> TABLETS**  
**(BUSPIRONE HYDROCHLORIDE)**  
**NDA 18-731/S-043 (SE-5)**

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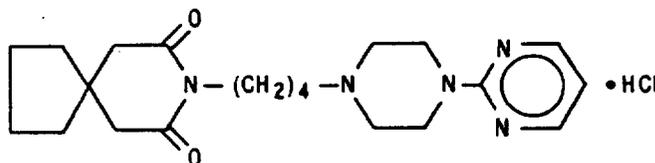
# BuSpar<sup>®</sup>

## (buspirone HCl, USP)

**(Patient Instruction Sheet Included)****DESCRIPTION**

BuSpar<sup>®</sup> (buspirone hydrochloride, USP) 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 as tablets for oral administration containing 5 mg, 10 mg, 15 mg, or 30 mg of buspirone hydrochloride, USP (equivalent to 4.6 mg, 9.1 mg, 13.7, and 27.4 mg of buspirone free base respectively). The 5-mg and 10-mg tablets are scored so they can be bisected. Thus, the 5-mg tablet can also provide a 2.5-mg dose, and the 10-mg tablet can provide a 5-mg dose. The 15-mg and 30-mg tablets are provided in the DIVIDOSE<sup>®</sup> tablet design. These tablets are scored so they can be either bisected or trisected. Thus, a single 15-mg tablet can provide the following doses: 15 mg (entire tablet), 10 mg (two thirds of a tablet), 7.5 mg (one half of a tablet), or 5 mg (one third of a tablet). A single 30-mg tablet can provide the following doses: 30 mg (entire tablet), 20 mg (two thirds of a tablet), 15 mg (one half of a tablet), or 10 mg (one third of a tablet). BuSpar Tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 30-mg tablet also contains iron oxide.

**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-HT<sub>1A</sub>) 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<sub>2</sub>-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<sub>max</sub>) 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. (see DOSAGE AND ADMINISTRATION section).

A multiple-dose study conducted in 15 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.

An *in vitro* protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone *in vivo*, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An *in vitro* study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.

Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by cytochrome P450 3A4 (CYP3A4). (See **PRECAUTIONS, Drug Interactions** section.) Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. 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 (buspirone hydrochloride) do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 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 <sup>14</sup>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.

### **Special Populations**

#### **Age and Gender Effects**

After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and  $C_{max}$ ) were observed between elderly and younger subjects or between men and women.

#### **Hepatic Impairment**

After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see **PRECAUTIONS** section).

#### **Renal Impairment**

After multiple-dose administration of buspirone to renally impaired ( $Cl_{CR} = 10-70$  mL/min/1.73 m<sup>2</sup>) patients, steady-state AUC of buspirone increased 4-fold compared with healthy ( $Cl_{CR} \geq 80$  mL/min/1.73 m<sup>2</sup>) subjects (see **PRECAUTIONS** section).

#### **Race Effects**

The effects of race on the pharmacokinetics of buspirone have not been studied.

### **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 everyday 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 (GAD). Many of the patients enrolled in these studies also had coexisting depressive symptoms and BuSpar relieved anxiety in the presence of these coexisting depressive symptoms. The patients evaluated in these studies had experienced symptoms for periods of 1 month to over 1 year prior to the study, with an average symptom duration of 6 months. Generalized Anxiety Disorder (300.02) is described in the American Psychiatric Association's Diagnostic and Statistical Manual, III<sup>1</sup> as follows:

Generalized, persistent anxiety (of at least 1 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, lightheadedness, 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. However, mild depressive symptoms are common in GAD.

The effectiveness of BuSpar in long-term use, that is, for more than 3 to 4 weeks, has not been demonstrated in controlled trials. There is no body of evidence available that systematically addresses the appropriate duration of treatment for GAD. However, in a study of long-term use, 264 patients were treated with BuSpar for 1 year 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**

**The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard.** There have been reports of the occurrence of elevated blood pressure when BuSpar (buspirone hydrochloride) has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

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 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 (buspirone hydrochloride) 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 (eg, 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 (ie, 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.
5. You should take BuSpar consistently, either always with or always without food.
6. During your treatment with BuSpar, avoid drinking large amounts of grapefruit juice.

### Laboratory Tests

There are no specific laboratory tests recommended.

### Drug Interactions

#### Psychotropic Agents

**MAO inhibitors:** It is recommended that BuSpar (buspirone hydrochloride) *not* be used concomitantly with MAO inhibitors (see **WARNINGS** section).

**Amitriptyline:** After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters ( $C_{max}$ , AUC, and  $C_{min}$ ) of amitriptyline or its metabolite nortriptyline were observed.

**Diazepam:** After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters ( $C_{max}$ , AUC, and  $C_{min}$ ) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

**Haloperidol:** In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.

**Nefazodone:** [see *Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)*]

**Trazodone:** There is one report suggesting that the concomitant use of Desyrel® (trazodone hydrochloride) and buspirone 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.

**Triazolam/Flurazepam:** Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.

**Other Psychotropics:** Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.

**Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)**

Buspirone has been shown *in vitro* to be metabolized by CYP3A4. This finding is consistent with the *in vivo* interactions observed between buspirone and the following:

**Diltiazem and Verapamil:** In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased AUC and  $C_{max}$  of buspirone 3.4-fold while diltiazem increased AUC and  $C_{max}$  5.3-fold and 4-fold, respectively.) Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.

**Erythromycin:** In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in  $C_{max}$  and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

**Grapefruit Juice:** In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in  $C_{max}$ ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.

**Itraconazole:** In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in  $C_{max}$  and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

**Nefazodone:** In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in  $C_{max}$  and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5-mg b.i.d. doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in  $C_{max}$  were observed for nefazodone (8%) and its metabolite HO-NEF (11%).

**Rifampin:** In a study in healthy volunteers, coadministration of buspirone (30 mg as a single dose) with rifampin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in  $C_{max}$ ; 89.6% decrease in AUC) and pharmacodynamic effects of buspirone. If the two drugs are to be used in combination, the dosage of buspirone may need adjusting to maintain anxiolytic effect.

**Other Inhibitors and Inducers of CYP3A4:** Substances that inhibit CYP3A4, such as ketoconazole or

ritonavir, may inhibit buspirone metabolism and increase plasma concentrations of buspirone while substances that induce CYP3A4, such as dexamethasone, or certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase the rate of buspirone metabolism. If a patient has been titrated to a stable dosage on buspirone, a dose adjustment of buspirone may be necessary to avoid adverse events attributable to buspirone or diminished anxiolytic activity. Consequently, when administered with a potent inhibitor of CYP3A4, a low dose of buspirone used cautiously is recommended. When used in combination with a potent inducer of CYP3A4 the dosage of buspirone may need adjusting to maintain anxiolytic effect.

#### Other Drugs

**Cimetidine:** Coadministration of buspirone with cimetidine was found to increase  $C_{max}$  (40%) and  $T_{max}$  (2-fold), but had minimal effects on the AUC of buspirone.

#### Protein Binding

*In vitro*, buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins. However, there has been one report of prolonged prothrombin time when buspirone was added to the regimen of a patient treated with warfarin. The patient was also chronically receiving phenytoin, phenobarbital, digoxin, and Synthroid®. *In vitro*, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.

Therapeutic levels of aspirin, desipramine, diazepam, flurazepam, ibuprofen, propranolol, thioridazine, and tolbutamide had only a limited effect on the extent of binding of buspirone to plasma proteins (see CLINICAL PHARMACOLOGY section).

#### 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 five 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

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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.

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### Pediatric Use

The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6-week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses studied were 7.5-30 mg b.i.d. (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.

### Geriatric Use

In one study of 6632 patients who received Buspar® for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients can-not be ruled out.

There were no effects of age on the pharmacokinetics of buspirone (see CLINICAL PHARMACOLOGY, Special Populations section.)

### Use in Patients With Impaired Hepatic or Renal Function

Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a lengthened half-life of buspirone. Therefore, the administration of BuSpar to patients with severe hepatic or renal impairment cannot be recommended (see CLINICAL PHARMACOLOGY section).

### 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 10% of the 2200 anxious patients who participated in the BuSpar premarketing clinical efficacy trials in anxiety disorders lasting 3 to 4 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 (buspirone hydrochloride) patients who participated in 4-week, controlled trials comparing BuSpar with placebo. The frequencies were obtained from pooled data for 17 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 nondrug 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 in the dose range for which BuSpar is being recommended (ie, 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 (buspirone hydrochloride) 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, involuntary movements, slowed reaction time, 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; 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.

### **POSTINTRODUCTION CLINICAL EXPERIENCE**

Postmarketing experience has shown an adverse experience profile similar to that given above. Voluntary reports since introduction have included rare occurrences of allergic reactions (including urticaria), angioedema, cogwheel rigidity, dizziness (rarely reported as vertigo), dystonic reactions, ataxias, extrapyramidal symptoms, dyskinesias (acute and tardive), ecchymosis, emotional lability, serotonin syndrome, transient difficulty with recall, urinary retention, and visual changes (including tunnel vision). Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar treatment has not been determined.

### **DRUG ABUSE AND DEPENDENCE**

#### **Controlled Substance Class**

BuSpar (buspirone hydrochloride) 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 (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

### **OVERDOSAGE**

#### **Signs and Symptoms**

In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with BuSpar alone.

Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD<sub>50</sub> values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 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 buspirone, and dialyzability of buspirone has not been determined.

### DOSAGE AND ADMINISTRATION

The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). 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 to 30 mg per day were commonly employed.

The bioavailability of buspirone is increased when given with food as compared to the fasted state (see **CLINICAL PHARMACOLOGY** section). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.

When buspirone is to be given with a potent inhibitor of CYP3A4 the dosage recommendations described in the **PRECAUTIONS: Drug Interactions** section should be followed.

### HOW SUPPLIED

BuSpar<sup>®</sup> (buspirone hydrochloride tablets, USP)

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 and 500, and in cartons containing 100 individually packaged tablets.

#### 5-mg tablets

NDC 0087-0818-41	Bottles of 100
NDC 0087-0818-44	Bottles of 500
NDC 0087-0818-43	Cartons of 100 unit dose

#### 10-mg tablets

NDC 0087-0819-41	Bottles of 100
NDC 0087-0819-44	Bottles of 500

Tablets, 15 mg white, in the DIVIDOSE<sup>®</sup> tablet design imprinted with the MJ logo, are available in bottles of 60 and 180. Tablets, 30 mg pink, in the DIVIDOSE<sup>®</sup> tablet design imprinted with the MJ logo, are available in bottles of 60. The 15-mg and 30-mg tablets are scored so that they can be either bisected or trisected. The 15-mg tablet has ID number 822 on one side and on the reverse side, the number 5 on each trisect segment. The 30-mg tablet has ID number 824 on one side and on the reverse side, the number 10 on each trisect segment.

NDA/Buspar/18731S43APLBL.doc

15-mg tablets

NDC 0087-0822-32

Bottles of 60

NDC 0087-0822-33

Bottles of 180

30-mg tablets

NDC 0087-0824-81

Bottles of 60

U.S. Patent Nos. 5,015,646 and 6,008,222

Store at Room Temperature—Protect from temperatures greater than 86° F (30° C). Dispense in a tight, light-resistant container (USP).

#### REFERENCE

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

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Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

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818DIM-15

1115202A3

Revised November 2000

**APPEARS THIS WAY  
ON ORIGINAL**

818DIM-15

1115202A3

**BuSpar<sup>®</sup>**

(buspirone HCl, USP)

Patient Instruction Sheet

**Rx only**

**HOW TO USE:**

**BuSpar<sup>®</sup>**

(buspirone HCl, USP)

**15-mg and 30-mg Tablets**

in convenient DIVIDOSE<sup>®</sup> tablet form

Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.

This DIVIDOSE tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages.

If your doctor prescribed the 30-mg tablet:

30 mg  
(the entire tablet)

20 mg  
(two thirds of a tablet)

10 mg  
(one third of a tablet)

15 mg  
(one half of a tablet)



If your doctor prescribed the 15-mg tablet:

15 mg  
(the entire tablet)

10 mg  
(two thirds of a tablet)

5 mg  
(one third of a tablet)

7.5 mg  
(one half of a tablet)

# 822 on 15-mg and  
824 on 30-mg tablet

To break a DIVIDOSE<sup>®</sup> tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo. Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).



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Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

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818DIM-15  
Revised May 2000

1115202A3

EXCLUSIVITY SUMMARY for NDA # 18-731/S-043

Trade Name BuSpar Generic Name bupirone tablets

Applicant Name Bristol-Myers Squibb HFD- 120

Approval Date July 19, 2001

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /X/

b) Is it an effectiveness supplement? YES /X/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE-5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_X\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_X\_/ NO /\_\_\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_X\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO /    /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-731 \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /    / NO /    /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_X\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/

If yes, explain: \_\_\_\_\_

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 125

Investigation #2, Study # 124

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____



(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # \_\_\_\_\_ YES /\_X\_/ NO /\_\_\_/ Explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
IND # \_\_\_\_\_ YES /\_X\_/ NO /\_\_\_/ Explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /\_X\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer

Date \_\_\_\_\_

Title: Regulatory Health Project Manager

\_\_\_\_\_  
Signature of Office of Division Director

\_\_\_\_\_  
Date

CC:  
Archival NDA  
HFD-120/Division File  
HFD-120/Homonnay  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

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Anna-Marie Homonnay  
9/14/01 02:46:18 PM  
CSO

Russell Katz  
9/17/01 10:50:08 AM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

*Homonnay*

**Pediatric Exclusivity Board**  
May 22, 2000

Pediatric Exclusivity Board Members  
Murray Lumpkin, OCD, Chair  
Dianne Murphy, Pediatrics Team  
Rosemary Roberts, Pediatrics Team  
Terrie Crescenzi, Pediatrics Team  
Leanne Cusumano, HFD-7  
Kim Dettelbach, GCF-1  
Mary Fanning, OGD  
MaryAnn Holovac, HFD-90

Review Division/Office Representatives  
Andrew Mosholder, HFD-120  
Kathy Smith, HFD-120  
Roberta Glass, HFD-120  
Anna Homonnay, HFD-120  
Rachel Behrman, HFD-40

**I. Pediatric Exclusivity Determination for Buspar (buspirone) by Bristol-Myers Squibb**

Initial Written Request: October 9, 1998  
Timeframe for submission of report of studies: May 14, 2000  
Date report of studies submitted: March 21, 2000  
Due Date for Pediatric Exclusivity Determination: June 19, 2000

- The studies were responsive to the Written Request.
- If granted, pediatric exclusivity will apply to all patents and exclusivity for the active moiety as well as any protection granted to supplement 043/18-731.

**Recommendations:** Grant pediatric exclusivity.

**Action Item:** Division was informed to notify the sponsor by phone that exclusivity has been granted.

Prepared by: */s/*  
Terrie L. Crescenzi

5/26/00  
Date

*/s/*  
Murray M. Lumpkin  
Chair, Pediatric Exclusivity Board

6/2/00  
Date

cc:  
Archival NDA 18-731  
HFD-120/Division File  
HFD-120/PM/Homonnay

CSO - ~~XXXXXXXXXX~~  
MAY 22 2000

### PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

#### PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 10/9/98 Application Written Request was made to: NDA/IND# 18-731  
 Timeframe Noted in Written Request for Submission of Studies 5/14/08  
 NDA# 18-731 Supplement # 3-043 Circle one: SE1 SE2 SE3 SE4 **SE5** SE6 SE7 SE8 SLR  
 Sponsor Bristol-Meyers Squibb  
 Generic Name bupropion HCl Trade Name Buprop Tablets  
 Strength 5, 10, 15, 30 mg Dosage Form/Route Tablets  
 Date of Submission of Reports of Studies 3/21/00  
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 6/21/00

Was a formal Written Request made for the pediatric studies submitted?	Y <input checked="" type="checkbox"/>
Were the studies submitted after the Written Request?	Y <input checked="" type="checkbox"/>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <input checked="" type="checkbox"/>
Was the timeframe noted in the Written Request for submission of studies met?	Y <input checked="" type="checkbox"/>
If there was a written agreement, were the studies conducted according to the written agreement?  OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <input checked="" type="checkbox"/>
Were the studies responsive to the terms of the Written Request?	Y <input checked="" type="checkbox"/>

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

#### PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity  **Granted**  **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
<u>18-731/001, 002</u>	<u>PATENT 4182763</u>	<u>22 MAY 2001</u>
	<u>PATENT 5015646</u>	<u>14 MAY 2008</u>

SIGNE IS/ DATE 5/22/00

cc:  
 Archival NDA/IND ##-###  
 HFD-xxx/division file  
 HFD-xxx/PM-CSO XXXXXXXXXX  
 120  
 HFD-93/Division of Data Management Services  
 HFD-600/Office of Generic Drugs  
 HFD-2/MLumpkin  
 HFD-104/DMurphy  
 HFD-600/Roberts 104-CEESCAN21

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** December 29 , 2000

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approvable Action for Pediatric Supplement for Buspar (buspirone); negative results for Buspar in the treatment of Generalized Anxiety Disorder (GAD) in pediatric patients

**TO:** File NDA 18-731/S-043  
[Note: This overview should be filed with the 3-20-00 original submission of this supplement.]

**1.0 BACKGROUND**

Buspirone is a 5HT1A antagonist that was approved for the treatment of anxiety on 9-29-86. Supplement 043 includes data from 2 safety and efficacy trials of buspirone in pediatric patients with GAD, and 2 PK studies, one in adults and one in pediatric patients. This supplement was submitted in support of a request for additional exclusivity under FDAMA. Although the 2 clinical trials failed to support efficacy, the sponsor has proposed labeling to describe the trial results.

Since the proposal was to use the currently approved Buspar formulations for this expanded population, there was no need for chemistry or pharmacology reviews. The primary review of the clinical efficacy and safety data was done by Andrew Mosholder, M.D. from the clinical group. Since the efficacy results were acknowledged to be negative by the sponsor, there was no need for a statistical review. The pharmacokinetic data were reviewed by Iftekar Mahmood, Ph.D. from OCPB.

The original supplement for this expanded indication (S-043) was submitted 3-20-00. There was no safety update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

## **2.0 CHEMISTRY**

As Buspar is a marketed product, there were no chemistry issues requiring review for this supplement.

## **3.0 PHARMACOLOGY**

As Buspar is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

## **4.0 BIOPHARMACEUTICS**

The sponsor conducted 2 PK studies in this program, 1 in pediatric patients (12 children and 12 adolescents) and 1 in adults (n=14). The design was the same for both, i.e., open label dose escalation: 3 days at 5 mg bid; 4 days at 7.5 mg bid; 7 days at 15 mg bid; 7 days at 30 mg bid. Overall, the results revealed somewhat higher exposures (C<sub>max</sub> and AUC) for both buspirone and 1-PP in children compared to adults given the same doses, but more similar exposures for adolescents and adults. In his review, Dr. Mahmood proposed a detailed summary of the PK findings under the Special Populations subsection of the Pharmacokinetics section of Clinical Pharmacology, as did the sponsor. Dr. Mosholder alternatively proposed a much briefer summary of the PK findings under the Pediatric Use subsection of Precautions, given the negative results of the efficacy studies. Generally, it has been Division policy that, when there is an absence of efficacy data in support of a pediatric claim, we have declined to provide PK information in pediatric patients, unless there is a specific reason to provide such data. In this case, the only reason to mention such data is to indicate that insufficient plasma levels could not have been an explanation for the negative efficacy findings. Thus, I agree with Dr. Mosholder's alternative approach regarding these PK data.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Summary of Studies 125 and 124**

Study 125 was a 6-week, randomized, double-blind, parallel group, placebo-controlled trial in pediatric outpatients (aged 6-17) with GAD. Approximately 110 patients were randomized to each of 3 groups (total randomized: n=341): buspirone 15-30 mg/day; buspirone 45-60 mg/day; or placebo. Dosing was on a bid basis. The primary outcome was change from baseline on the sum of scores for 4 items on the C-KSADS-GAD that are specific to anxiety, i.e., severity of anxiety and worry, difficulty controlling the worry, severity of associated symptoms, and global distress about

symptoms. Overall, the sample included about 60% females, about 90% Caucasians, and the mean age was about 14. The results were negative, with p-values on the primary outcome for drug vs placebo for the LOCF analysis as follows: low dose (p=0.31); high dose (p=0.47). The results were similarly negative for the primary outcome in the OC analysis, and for CGI severity and improvement on both LOCF and OC analyses. Only one subgroup analysis was significant, i.e., for adolescents for the low dose group.

Study 124 was a 6-week, randomized, double-blind, parallel group, placebo-controlled trial in pediatric outpatients (aged 6-17) with GAD. Approximately 115 patients were randomized to each of 2 groups (total randomized: n=227): buspirone 15-60 mg/day; or placebo. Dosing was on a bid basis. The primary outcome was change from baseline on the sum of scores for 4 items on the C-KSADS-GAD that are specific to anxiety, i.e., severity of anxiety and worry, difficulty controlling the worry, severity of associated symptoms, and global distress about symptoms. Overall, the sample included about 50% females, about 90% Caucasians, and the mean age was about 11. As for study 125, the results were negative, with a p-value on the primary outcome for drug vs placebo for the LOCF analysis as follows: p=0.15. The results were also negative for the primary outcome in the OC analysis, but showing more of a trend (p=0.07). However, the results for CGI severity and improvement, on both LOCF and OC analyses, were clearly negative. Subgroup analyses based on stratifying for children and adolescents also revealed no positive findings.

### **5.1.2 Conclusions Regarding Efficacy Data**

Neither study supported a claim of effectiveness for buspirone in pediatric GAD. Given that these patients likely had exposures to buspirone and 1-PP equal to or higher than what would be seen in adults given these same doses, i.e., doses shown to be effective in adults with GAD, under-dosing is not an explanation for these negative findings. Sample size should also have been adequate. It should be recalled, however, that the development program for buspirone in adults with GAD included a number of negative studies, thus, this finding of 2 negative studies in pediatric patients is not definitive evidence that buspirone is not effective in this subgroup. Nevertheless, these findings need to be noted in labeling.

## **5.2 Safety Data**

Dr. Mosholder has reviewed the relatively small amount of additional safety data for buspirone in pediatric patients with GAD. The total buspirone-exposed sample with safety assessments was n=359. Essentially there were no surprises and no findings suggestive of any unique pattern of risk in this subgroup. However, the data were relatively short-term, and did not include analyses of weight change.

## **5.3 Clinical Sections of Labeling**

The sponsor's proposed labeling for this supplement included additions to several sections, as follows:

- PK findings under a Special Populations subsection of Clinical Pharmacology
- Negative efficacy findings under a new Clinical Studies in Special Populations subsection of Clinical Pharmacology
- A summary of the PK, efficacy, and safety findings under the Pediatric Use subsection of Precautions
- The safety findings under a Pediatric Clinical Experience subsection of Adverse Reactions
- Dosing advice regarding what is a tolerated dose under a Pediatric Patients subsection of Dosage and Administration

Dr. Mosholder has argued that, given the negative outcome for the 2 efficacy studies, it would be more appropriate to summarize the findings more briefly under the Pediatric Use section. He has proposed a brief summary for this section. I agree with his argument and with his proposed language for this statement.

## **6.0 WORLD LITERATURE**

Dr. Mosholder reviewed the 4 literature reports provided for this supplement. These reports did not include any important new safety information regarding the use of buspirone in pediatric patients.

## **7.0 FOREIGN REGULATORY ACTIONS**

I am not aware of any foreign regulatory actions regarding the use of buspirone in pediatric patients.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this supplement to the PDAC.

## **9.0 DSI INSPECTIONS**

To my knowledge, no inspections were done for this supplement.

## **10.0 APPROVABLE LETTER**

An approvable letter acknowledging our decision to proceed with a minor labeling change to acknowledge the negative results of this program has been included with the approvable package.

**11.0 CONCLUSIONS AND RECOMMENDATIONS**

The results of this negative program for buspirone in pediatric GAD should be noted in labeling. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

cc:  
Orig NDA 20-822/S-009  
HFD-120/Division File  
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

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**APPEARS THIS WAY  
ON ORIGINAL**

## REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-731 SE5-043  
SPONSOR: BRISTOL-MYERS SQUIBB COMPANY  
DRUG: Buspirone HCl (BuSpar)  
MATERIAL SUBMITTED: Pediatric Supplement SE5-043  
DATE SUBMITTED: 3/20/00  
DATE RECEIVED: 3/21/00  
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### BACKGROUND

In response to a Pediatric Exclusivity Written Request issued by FDA on 10/9/98, Bristol-Myers Squibb has submitted this pediatric supplement. (Note that the sponsor has already been granted the sixth months of pediatric patent exclusivity in exchange for fulfilling the Written Request by submitting this supplement.) This supplement contains data from the following studies: a pharmacokinetic study with pediatric patients, a pharmacokinetic study with adults (for comparative purposes), and two randomized, double blind, placebo controlled pediatric trials for the indication of generalized anxiety disorder (GAD).

### SPONSOR'S PROPOSED LABELING

#### Under Clinical Pharmacology—Special Populations

##### Pediatric Patients

At steady state, following doses of 7.5, 15, and 30 mg b.i.d., children (aged 6-12 years) had a mean buspirone C<sub>max</sub> that was 2.9-fold, 2.1-fold, and 1.7-fold higher than that of adults, respectively. The mean buspirone AUC in children at these doses was 1.8-fold, 1.5-fold, and 1.1-fold higher, respectively. Across the dose range studied, the C<sub>max</sub> and AUC of 1-PP in children were approximately double those of adults. Adolescents (aged 13-17 years) had higher mean buspirone C<sub>max</sub> than adults at 7.5 and 15 mg b.i.d. doses (2.3-fold and 1.5-fold higher, respectively), but not at the 30 mg b.i.d. dose where their C<sub>max</sub> was only 10% higher than adults. In adolescents at doses of 7.5 and 15 mg b.i.d., the mean AUC was 1.8-fold and 1.2-fold higher than that of adults, while at 30 mg b.i.d. it was 20% lower. Adolescents tended to have a C<sub>max</sub> and AUC of 1-PP similar to adults.

#### Under Clinical Pharmacology—Clinical Studies in Special Populations

The effectiveness of buspirone in pediatric patients (ranging from 6 to 17 years of age) with Generalized Anxiety Disorder (GAD) (American Psychiatric Association's Diagnostic and Statistical Manual IV [DSM-IV]) was evaluated in two placebo-controlled trials of six weeks duration. In these studies, 334 patients received buspirone in doses of 7.5-30 mg b.i.d., and 225 patients received placebo. Differences between buspirone and placebo treatment groups for the primary efficacy measure (C-KSADS GAD module ratings scale using four items: Severity of Anxiety and Worry; Difficulty Controlling the Worry; Severity of Associated Symptoms; and Global Distress about Symptoms) in individual studies were not statistically significant. The results of a post-hoc meta-analysis showed statistical significance over placebo for the primary efficacy measure in the adolescent age group (12-17 years); results in children (6-11 years) were not statistically significant, but favored buspirone over placebo. There are no long-term efficacy data in pediatric patients. See also ADVERSE REACTIONS: Pediatric Clinical Experience.

### Under Precautions—Pediatric Use

The safety and effectiveness of buspirone were evaluated in two placebo-controlled trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD (DSM-IV<sup>1</sup>). Differences in efficacy variables between buspirone and placebo treatment groups were not statistically significant in each individual study (see CLINICAL STUDIES IN SPECIAL POPULATIONS). Buspirone was generally well tolerated at doses of 15-60 mg/day for up to six weeks in these studies. It should be noted that plasma exposure to buspirone and its active metabolite, 1-PP, was higher in pediatric patients compared to adults given equivalent doses (see CLINICAL PHARMACOLOGY, Special Populations). There were no serious adverse events or unexpected safety findings attributed to buspirone. The most common ( $\geq 5\%$ ) adverse events that occurred more frequently than with placebo ( $>2$  times the placebo rate) were lightheadedness and somnolence. (See ADVERSE REACTIONS: Pediatric Clinical Experience.) There are no long-term safety or efficacy data in this population.

### Under Adverse Events

#### Pediatric Clinical Experience

Buspirone was generally well tolerated in two placebo controlled trials involving 334 buspirone-treated pediatric patients (ranging from 6 to 17 years of age) with GAD (DSM-IV<sup>1</sup>); doses were 7.5-30 mg b.i.d. (15-60 mg/day) for up to six weeks. It should be noted that plasma exposure to buspirone and its active metabolite, 1-PP, was higher in pediatric patients compared to adults given equivalent doses (see CLINICAL PHARMACOLOGY, Special Populations). There were no serious adverse events or unexpected safety findings attributed to buspirone. The most common ( $> 5\%$ ) adverse events that occurred more frequently than with placebo ( $>2$  times the placebo rate) were lightheadedness and somnolence. The table below shows the adverse events that occurred at a frequency of 5% or more among buspirone-treated patients in these trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS IN PEDIATRIC PATIENTS (Percent of Patients Reporting)		
Adverse Experience	Buspirone (n=334)	Placebo (n=225)
Body as a Whole		
Headache	29	23
Asthenia	10	8
Accidental Injury	7	7
Digestive System		
Nausea	16	10
Dyspepsia	13	12
Vomiting	6	7
Diarrhea	5	7
Nervous System		
Lightheadedness	34	5
Somnolence	14	4
Insomnia	5	7
Nervousness	5	3
Respiratory System		
Upper Respiratory Infection	5	5
Rhinitis	5	3

Among the 334 patients treated with buspirone, approximately 4% discontinued treatment due to an adverse event compared to  $<1\%$  of the placebo-treated pediatric patients. The majority of these discontinuations occurred in patients receiving buspirone 45-60 mg/day. The more common events causing discontinuation were nausea and lightheadedness. There are no long-term safety data in this population.

### Under Dosage and Administration

**Pediatric Patients**—Although the efficacy of buspirone has not been established in this population, doses of buspirone ranging from 7.5-30 mg b.i.d. (15-30 mg/day) were generally well tolerated (see CLINICAL STUDIES IN SPECIAL POPULATIONS and ADVERSE REACTIONS: Pediatric Clinical Experience).

### Financial Disclosure Information

Dr. Geoffrey Dunbar certified on the Form 3454 that Bristol-Myers Squibb Company did not enter into any financial arrangements with the investigators that might have influenced the outcome of the studies. This applied only to the two efficacy trials; the pharmacokinetic studies were not considered "covered clinical studies" for the financial disclosure requirement.

### CLINICAL DATA SOURCES

The table below summarizes the studies submitted with this supplement.

Study	Description
CN101-123	Open label, dose escalation, 21 day pharmacokinetic study; n= 25 pediatric subjects
CN101-129	Same as CN101-123; n= 14 adult volunteers
CN101-124	Multicenter, randomized, double blind, placebo controlled, 6 week trial; buspirone 15-60 mg/day (flexible dosing) versus placebo; n=227 pediatric subjects with GAD
CN101-125	Multicenter, randomized, double blind, placebo controlled, 6 week trial; buspirone 15-30 and 45-60 mg/day versus placebo; n=341 pediatric subjects with GAD

For the integrated pediatric safety data base, the sponsor included data from studies 123, 124 and 125. The following is a summary of the demographic characteristics of the patients.

### Summary of patient characteristics, pediatric safety database

TREATMENT GROUP	Buspirone	Placebo
TOTAL SUBJECTS RANDOMIZED	363	230
AGE RANGE, YRS	6-17	6-17
MALES, N	158	98
FEMALES, N	205	132
BLACK, N	23	9
HISPANIC, N	18	6
CAUCASIAN, N	315	208
OTHER ETHNICITY, N	7	7

The mean age for subjects in the two double blind trials was approximately 11 years in all treatment groups. As seen above, the sample was predominantly caucasian and female.

### PHARMACOKINETIC FINDINGS

In study 123, a total of 25 children and adolescents with anxiety disorders received open label buspirone at increasing dosages, on the following schedule:

1<sup>st</sup> week: 5 mg BID x 3 days, then 7.5 mg BID x 4 days  
 2<sup>nd</sup> week: 15 mg BID x 7 days  
 3<sup>rd</sup> week: 30 mg BID x 7 days

On the last day of each week, multiple pharmacokinetic blood samples were obtained. The sponsor conducted a similarly designed pharmacokinetic study with 14 healthy adult volunteers, study 129.

The tables below show the pharmacokinetic results for studies 123 and 129.

**Mean Buspirone C<sub>max</sub> (ng/ml) (CV)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	0.67 (83%)	0.54 (113%)	0.23 (70%)
15 mg BID	1.96 (109%)	1.44 (143%)	0.93 (56%)
30 mg BID	3.96 (58%)	2.64 (107%)	2.36 (65%)

**Mean Buspirone AUC 0-tau (ng hr/ml) (CV)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	1.48 (83%)	1.50 (102%)	0.82 (94%)
15 mg BID	4.80 (99%)	3.94 (120%)	3.19 (51%)
30 mg BID	10.3 (50%)	7.51 (99%)	9.22 (69%)

**Mean Buspirone t<sub>1/2</sub> (hr) (SD)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	2.0 (0.9)	2.9 (1.5)	3.4 (0.8)
15 mg BID	3.1 (0.7)	3.4 (1.3)	3.5 (1.2)
30 mg BID	2.7 (0.9)	3.4 (1.1)	3.4 (1.1)

**Mean 1-PP C<sub>max</sub> (ng/ml) (CV)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	7.0 (56%)	3.8 (51%)	3.1 (50%)
15 mg BID	13.1 (42%)	7.8 (46%)	6.6 (42%)
30 mg BID	22.1 (25%)	15.7 (41%)	12.7 (44%)

**Mean 1-PP AUC 0-tau (ng hr/ml) (CV)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	41 (78%)	20 (72%)	19 (64%)
15 mg BID	77 (56%)	44 (60%)	43 (59%)
30 mg BID	137 (31%)	85 (53%)	90 (56%)

**Mean 1-PP t<sub>1/2</sub> (hr) (SD)**

Dose	Children (n=12)	Adolescents (n=12)	Adults (n=14)
7.5 mg BID	4.5 (1.9)	3.7 (1.3)	4.2 (1.2)
15 mg BID	4.2 (1.1)	4.3 (1.3)	4.4 (1.4)
30 mg BID	3.9 (0.7)	3.8 (1.0)	4.7 (1.4)

Based on these results, the sponsor concluded that for a specific dose of buspirone, children had generally higher exposures than adults on average, while adolescent pharmacokinetic values were closer to those of adults. There is considerable variability in the data for both pediatric and adult subjects. The sponsor did not present an analysis using weight-normalized dosages (mg/kg).

#### **EFFICACY FINDINGS**

As noted previously, there were two placebo controlled studies relevant to the question of efficacy in pediatric patients, studies 124 and 125. Study 125 included a comparison of a high dose range (45-60 mg) to a low dose range (15-30 mg) while study 124 employed flexible buspirone dosing. I will summarize the results of each separately.

#### **Study 125**

##### **Investigators**

There were 48 investigators for this trial, of which 32 actually enrolled subjects. The sponsor's listing of investigators is reproduced below.

**INVESTIGATORS AND STUDY CENTERS:** Anne Marie Albano, PhD, NYU Child Study Center, New York, NY; Scott Balogh, MD, Augusta, GA; Jeffrey Blumer, MD, PhD, Rainbow Babies and Children's Hospital, Cleveland, OH; Joan Busner, PhD, St. Louis University School of Medicine, St. Louis, MO; Joshua Calhoun, MD, Unity Health Research, St. Louis, MO; John Dunphy, Oregon Research Group, Eugene, OR; Thomas Eppright, MD, University of Missouri-Columbia, Columbia, MO; Carlos Figueroa, MD, Advanced Psychiatric Group, Rosemead, CA; Daniel Grosz, MD, Pharmacology Research Institute, Northridge, CA; Thomas Gualtieri, MD, North Carolina Neuropsychiatry, Chapel Hill, NC; David Harmon, DO, River Valley Behavioral Health, Owensboro, KY; Robert Hendren, DO, Robert Woods Johnson Medical School, Piscataway, NJ; Donna Holland, MD, Boca Raton Medical Research, Boca Raton, FL; Christopher Kelsey, MD, San Diego Center for Research, San Diego, CA; Arif Khan, MD, Northwest Clinical Research Center, Bellevue, WA; Irving Kolin, MD, Winter Park, FL; Henrietta Leonard, MD, Rhode Island Hospital, Providence, RI; Alan Levine, MD, Denver Center for Medical Research, Denver, CO; Peter Lomborg, MD, Seattle, WA; Anne Macek, MD, Institute for Advanced Clinical Research, Elkins Park, PA; John Murphy, Southwestern Research Institute, Beverly Hills, CA; Donna Palumbo, PhD, University of Rochester, Rochester, NY; Cynthia Pfeffer, MD, New York Hospital, White Plains, NY; Elizabeth Reeve, MD, Regions Hospital, St. Paul, MN; Robert Reichler, MD, Pacific Institute of Mental Health, Seattle, WA; Mark Riddle, MD, Johns Hopkins Medical Institutions, Baltimore, MD; Michael Rieser, MD, Lexington, KY; Adelaide Robb, MD, Children's National Medical Center, Washington, DC; Murray Rosenthal, DO, Behavioral and Medical Research, San Diego, CA; R. Bart Sangal, MD, Clinical Neurophysiology Associates, Troy, MI; Keith Saylor, PhD, Pediatric Trial Center, Rockville, MD; Karen Wagner, MD, PhD, University of Texas Medical Branch, Galveston, TX.

##### **Design**

The purpose of this study was to evaluate the safety and efficacy of buspirone in pediatric patients with GAD. This was a 6 week, randomized, double blind, parallel group, placebo controlled trial. The planned sample was 210 outpatients with GAD, aged 6-17 years, with a Schedule for Affective Disorders and Schizophrenia for School Age Children-GAD module-Columbia version (C-KSADS-GAD) score of at least 16. Exclusion criteria included a score of 45 or higher on the Childhood Depression Rating Scale (CDRS), IQ less than 70, pregnancy, lactation, major

psychiatric illnesses other than GAD, and use of other psychotropic drugs. The primary outcome variable was originally the combined score for the two items severity of anxiety and worry and global impairment of functioning on the C-KSADS-GAD. In a telecon 12/7/99 with our Division, it was agreed to use a more specific set of 4 items for the primary outcome measure: severity of anxiety and worry, difficulty controlling the worry, severity of associated symptoms, and global distress about symptoms. Secondary outcome measures included CGI-severity and CGI-improvement, Children's Anxiety Ratings Scale (CARS) and Screen for Child Anxiety Related Emotional Disorders (SCARED). Screening of subjects included history and physical exam, ECG, clinical laboratories, CDRS, and Kaufman Brief Intelligence Test. Eligible subjects were randomized to one of three treatments (equal randomization ratio): buspirone 15-30 mg/d, buspirone 45-60 mg/d, and placebo. Medication was given in divided doses (b.i.d.). Subjects were titrated to their assigned dose range, and were assessed on treatment at weeks 1, 2, 3, 4, and 6. Safety monitoring included vital signs and a repeat of the ECG and clinical laboratories at the end of the study.

### Results

Sample characteristics: There were 116 patients randomized to placebo, 114 to low-dose buspirone and 111 to high-dose buspirone. The mean age was approximately 11 years for all three groups. Females predominated in all three groups (by approximately 60% to 40%), and the vast majority (~90%) of subjects were caucasian. The table below shows the patient disposition (by number of patients in each category).

Treatment group	Placebo	Buspirone 15-30 mg/d	Buspirone 45-60 mg/d
Randomized	116	114	111
Completed	101	102	90
Discontinuations	15	12	21
Adverse event	-	2	11
Lack of efficacy	1	1	0
Withdrew consent	6	2	4
Patient Unreliability	0	4	3
Lost to follow up	5	2	2
Other	3	1	1

Note the more frequent dropouts for adverse events among the high dose group, and the small number of dropouts for lack of efficacy in all 3 groups.

As specified in the protocol, the sponsor analyzed an "efficacy sample" including all subjects randomized who received at least one dose of medication and had at least one efficacy assessment that was no more than seven days after the last dose of medication. Results for the primary efficacy measure are shown below.

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Treatment group	Placebo	Buspirone 15-30 mg/d	Buspirone 45-60 mg/d
<u>Efficacy sample (N)</u>	112	112	109
Mean score at baseline, primary outcome	17.9	18.1	18.0
Week 6, mean change from baseline, primary outcome, LOCF (p-value vs. pbo)	-4.9	-5.7 (p=0.31)	-5.4 (p=0.47)
Week 6, mean change from baseline, primary outcome, OC(p-value vs. pbo)	-5.0	-5.9 (p=0.18)	-5.7 (p=0.31)
Week 6, mean CGI-improvement, LOCF (p-value versus placebo)	3.4	3.2 (p=0.27)	3.3 (p=0.47)
Week 6, mean CGI-improvement, completers (p-value vs. pbo)	3.4	3.1 (p=0.21)	3.1 (p=0.21)
Week 6, mean change from baseline, CGI-severity, LOCF (p-value vs. pbo)	-1.1	-1.3 (p=0.42)	-1.3 (p=0.61)
Week 6, mean change from baseline, CGI-severity, OC (p-value vs. pbo)	-1.2	-1.4 (p=0.25)	-1.4 (p=0.21)

A subgroup analysis of adolescent subjects showed a statistically significant effect of buspirone on the primary outcome variable, but only for the low dose group. No drug-placebo comparisons were statistically significant for the subgroup of children.

On the SCARED and CARS scores there were no results favoring either dose of drug over placebo.

Conclusions: The subgroup analysis suggested some effect of the drug in adolescents, but this result would be more credible if it were not limited to just the lower dose group alone. On balance, this trial provides no evidence that buspirone has any effect on pediatric GAD symptoms.

Study 124

Investigators

There were a total of 34 investigators for this trial, of which 25 actually enrolled patients. The sponsor's listing of investigators and sites is reproduced below.

**APPEARS THIS WAY  
ON ORIGINAL**

**INVESTIGATORS AND STUDY CENTERS:** Daniel Anderson, MD, PsychAlliance Research Inc., Lakewood, CA; Mohammed Bari, MD, Synergy Research Center, Chula Vista, CA; Gail Bernstein, MD, University of Minnesota Medical School, Minneapolis, MN; Joseph Bryer, MD, Meadow Wood Hospital, New Castle, DE; Bruce Corser, MD, Community Research Management Associates, Cincinnati, OH; Henry Crabbe MD, PhD, Psychiatric Medicine Center, New London, CT; Jonathan Dowben MD, University of Alabama at Birmingham, Birmingham, AL; Graham Emslie, MD, University of Texas Southwestern Medical Center, Dallas, TX; Gary Gerard, MD, Neurology Center of Ohio, Toledo, OH; Howard Hassman, MD, Comprehensive Clinical Research, Berlin, NJ; Jeffrey Hirschfield, MD, Clinical Research of West Florida, Clearwater, FL; Glen Koch, MD, QualSite Clinical Research, Wheat Ridge, CO; Michael Levin, MD, Berkeley, CA; Thomas Marbury, MD, Orlando Clinical Research Center, Orlando, FL; Paul Markovitz, MD, PhD, Mood and Anxiety Research and Treatment Center, Beachwood, OH; Jeffrey Mattes, MD, Psychopharmacology Research Association of Princeton, Princeton, NJ; Robert Mitchell Jr., MD, Dominion Psychiatric Associates, Virginia Beach, VA; Lori Nesbitt, PharmD, Gulf Coast Clinical Services, Mobile, AL; Ani Patel, MD, Damluji Research Center, Vista, CA; Ira Pinnelas, MD, Physician Associates of Florida, Maitland, FL; V. Sharma, MD, Mount Sinai Medical Center, New York, NY; Robert Sholtes, MD, MacNeal Center for Clinical Research, Berwyn, IL; Malcolm Sperling, MD, Edinger Medical Group, Fountain Valley, CA; Yogendra Upadhyay, MD, South Oaks Hospital, Amityville NY; Michelle Ware-Stephens, MD, IPS Research, Oklahoma City, OK

## Design

The purpose of this trial, as with the previously described trial, was to assess the safety and efficacy of buspirone in the treatment of pediatric GAD. This was a 6 week, randomized, double blind, parallel group, placebo controlled trial. The intended sample was 140 outpatients, aged 6-17 years, with GAD. This trial was identical in design to study 125 in most respects. The differences were in the double blind treatment groups; subjects were randomized (in a 1:1 ratio) to either placebo or flexibly dosed buspirone 15-60 mg/d, administered b.i.d. For other aspects of the design and analysis plan, the reader is referred to the description of study 125, above.

## Results

**Sample characteristics:** The mean age for both groups was roughly 11 years, and both treatment groups had approximately equal numbers of males and females. The sample was overwhelmingly caucasian (>90% in both groups).

The overall disposition of subjects is shown in the table below.

Treatment group	Placebo	Buspirone 15-60 mg/d
Randomized	114	113
Completed	105	100
Discontinuations		
Adverse event	1	2
Lack of efficacy	1	0
Withdrew consent	5	6
Patient Unreliability	0	3
Lost to follow up	1	2
Other	1	0

The following table presents the efficacy results for selected outcome measures.

Treatment group	Placebo	Buspirone 15-60 mg/d
Efficacy sample (N)	111	111
Completed (n)	104	100
Mean score at baseline, primary outcome measure	17.7	18.1
Week 6, mean change from baseline, primary outcome, LOCF (p-value vs. pbo)	-4.6	-5.6 (p=0.15)
Week 6, mean change from baseline, primary outcome, OC (p-value vs. pbo)	-4.6	-5.9 (p=0.07)
Week 6, mean CGI-improvement, LOCF (p-value versus placebo)	3.5	3.3 (p=0.42)
Week 6, mean CGI-improvement, completers (p-value vs. pbo)	3.4	3.2 (p=0.27)
Week 6, mean change from baseline, CGI-severity, LOCF (p-value vs. pbo)	-1.1	-1.2 (p=0.37)
Week 6, mean change from baseline, CGI-severity, OC (p-value vs. pbo)	-1.1	-1.3 (p=0.21)

On the SCARED and CARS scales there were no results favoring drug over placebo. Also, for the primary outcome measure, a subgroup analysis by age category (6-11 years and 12-17 years) did not yield any favorable drug-placebo comparisons.

**Conclusions:** The most favorable result for the drug group in comparison to placebo appeared with the observed cases analysis for the primary outcome measure, but this did not reach statistical significance. Unlike the previous study, the lack of effect was uniform between the older and younger subgroups. On balance, this trial did not yield any evidence that buspirone is active against pediatric GAD symptoms.

**Overall conclusions regarding efficacy:** Neither of these placebo-controlled trials yielded evidence that buspirone is active against the symptoms of pediatric GAD. Given the number of subjects enrolled, inadequate sample size is not a likely explanation. The lack of effect in comparison to placebo was consistent across various outcome measures, so that choice of a different primary outcome variable in the analysis plan would not have changed the findings for either study.

#### **SAFETY FINDINGS**

The sample available for safety analysis was slightly smaller than the total number entered in the trials (n=359 for buspirone and n=225 for placebo), presumably because a few subjects were lost to follow up.

The table below summarizes the patient disposition.

Category	Buspirone (no. pts.)	Placebo (no. pts.)
Total n	363	230
Completed	313	206
Discontinuations		
Adverse events	17	1
Lack of efficacy	1	2
Withdrew consent	11	14
Patient unreliable	10	0
Lost to follow up	6	6
Other	2	4

Eleven of the 17 subjects who discontinued for adverse events were assigned to the high dose group in study 125 (i.e., 45-60 mg/d).

#### Serious adverse events

There were no deaths in these studies. There were 3 serious adverse events in buspirone treated patients, listed below.

- Subject 029/157, a 10 y.o. male, underwent surgery for blockage of right ureter.
- Subject 037/388, an 8 y.o. male, was hospitalized for aggressive behavior.
- Subject 029/156, a 14 y.o. female, took an overdose of multiple medications in a suicide attempt (16 days after the final dose of study medication).

#### Adverse events associated with discontinuations

The adverse events associated with discontinuation of buspirone, out of the safety sample of 359 subjects, are listed below with the numbers of patients who dropped out for each event. More than one adverse event may be listed per subject who discontinued. One placebo patient dropped out with neurosis.

Two of the adverse dropouts occurred in the pharmacokinetic study. One of these two dropouts (#102, a 6 year old black male who dropped out with vomiting, diarrhea and abdominal pain) had the highest AUC for buspirone and I-PP of all the subjects in the pharmacokinetic study.

<u>Adverse event</u> associated with dropout	<u>Number of subjects (total subjects=17)</u>
Lightheadedness	10
Nausea	7
Headache	2
Pain abdomen	2
Vomiting	2
Somnolence	2
Abnormal stool	1
Diarrhea	1
Anxiety	1
Hyperactivity	1
Rash	1
Abnormal vision	1

Note that lightheadedness and nausea were among the more commonly reported adverse events associated with discontinuation in adult clinical trials.

#### Adverse event incidence

The sponsor provided a pooled analysis using data from the two placebo controlled studies. By the usual criteria for considering an adverse event common and drug-related (i.e., incidence  $\geq 5\%$  and relative risk versus placebo  $\geq 2$ ), the adverse events lightheadedness and somnolence fit this description. Lightheadedness was reported in 34% of buspirone patients and 5% of placebo patients, while somnolence was reported in 14% of buspirone patients and 4% of placebo patients. For comparison, in the adult trials described in the BuSpar labeling, the common and drug related adverse events were dizziness, nervousness and headache.

#### Clinical laboratories

The sponsor used predetermined criterion values for defining laboratory abnormalities as potentially clinically significant. A total of 12 buspirone patients in these studies had such abnormalities. The table below shows the number of laboratory abnormalities for the clinical studies. In my view, these findings did not suggest any laboratory abnormalities associated with buspirone use. The sponsor did not perform an analysis of central tendency for laboratory parameters.

Laboratory abnormality	Number of patients with abnormality	
	Placebo (n=224)	Buspirone (n=359)
Eosinophilia	3	5
Proteinuria	4	4
Inc. total bilirubin	2	2
Dec. hematocrit	2	1

#### Vital Signs

The sponsor identified criterion values for defining vital signs as clinically significant. These values were slightly different for ages 6-12 and ages 13-17, which is appropriate. The table below shows the incidence in the clinical studies. There did not appear to be an association with buspirone for any abnormality. The sponsor did not perform an analysis of central tendency for vital sign measurements. Also, although weights were obtained in all three studies, the sponsor did not provide an analysis of weight data.

Vital sign abnormality	Number of patients with abnormality	
	Placebo (n=224)	Buspirone (n=359)
↑ pulse	0	1
↓ pulse	1	0
↑ systolic bp	5	7
↓ systolic bp	5	2
↑ diastolic bp	4	7
↓ diastolic bp	4	3

### Electrocardiograms

The sponsor also established predetermined criteria for designating ECG abnormalities as potentially clinically relevant. Among buspirone treated children and adolescents in these studies, there were the following ECG abnormalities observed: nonspecific ST/T, widened QRS interval, low heart rate (in 2 subjects), supraventricular beat (in 2 subjects), increased QTc interval (from 428 msec baseline to 485 msec on day 42). These abnormalities do not suggest a pattern of ECG changes associated with buspirone treatment. The sponsor did not perform an analysis of central tendency for ECG parameters.

### Overall conclusions regarding safety data

The data in this supplement does not suggest any unique pattern of adverse reactions to buspirone in pediatric subjects. It should be borne in mind that these data are limited to short term exposure; also, no analysis of weight data was provided, nor were there any analyses of central tendency for vital signs, laboratory or ECG parameters.

### Literature search

The sponsor conducted a literature search which revealed 4 publications concerning the use of buspirone for pediatric GAD. Two were reports of open label trials, and two were single case reports. These articles did not include any important new information about safety (or efficacy).

### CONCLUSIONS AND RECOMMENDATIONS

The data presented in this supplement do not support the efficacy of buspirone in the treatment of pediatric GAD. (The sponsor argues that a meta-analysis suggests an effect in the adolescent subgroup, but I do not find this persuasive because of the post-hoc nature of this analysis.) There were no safety findings unique to the pediatric age group from these trials, although the sponsor's safety analyses had certain limitations, as discussed above. Based on the results obtained in the pediatric pharmacokinetic trial, the plasma concentrations of buspirone and its active metabolite (1-PP) should have equaled or exceeded the exposures seen in adults receiving dosages in the same range; thus, under-dosing is not a likely explanation for the lack of drug effect in the two double blind studies.

With respect to labeling, I agree with the sponsor's proposal to note the results of the studies in the BuSpar labeling. However, given the negative results of these trials, I do not feel it is appropriate to add statements regarding the pediatric data other than under Precautions—Pediatric Use. My proposed labeling is shown below.

### Medical Officer's proposed labeling and comments for sponsor

[You have proposed labeling changes and additions for the following sections and subsections:

Clinical Pharmacology/Special Populations/Pediatric Patients  
Clinical Pharmacology/Clinical Studies in Special Populations  
Precautions/Pediatric Use  
Adverse Reactions  
Dosage and Administration.

However, in view of the failure of either study 124 or 125 to show efficacy of buspirone in the pediatric population, we believe the labeling changes should be confined to the Precautions/Pediatric Use section. We have omitted the changes from the other sections, and we propose the following language for the Pediatric Use subsection, based on your proposal.]

Under Precautions—Pediatric Use

The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6 week trials, involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. When compared to placebo, there was no efficacy of buspirone on the symptoms of GAD in either study, using doses equal to those for adults (15-60 mg/day for up to six weeks). Pharmacokinetic studies have shown that for identical doses, plasma exposures to buspirone and its active metabolite, 1-PP, are higher in pediatric patients than adults. Therefore, inadequate dosing is unlikely to be the explanation for the lack of effect in these trials. No unexpected safety findings were associated with buspirone in these studies. There are no long-term safety or efficacy data in this population.

*/S/*  
Andrew Mosholder, M.D.  
Medical Officer, HFD-120

NDA 18-731 SE5-043  
Div file  
HFD-120 Laughren, Homonnay, Mosholder

11-25-00

I agree that we can proceed with an  
approvable action, i.e., for labeling  
revealing no demonstrated benefit  
in pediatric patients with GAD. See  
items to file for more detailed  
response.

*/S/*  
TL, ADP

Buspirone Tablets  
NDA 18-731/S-043

Bristol-Myers Squibb  
Research Parkway, Wallingford, CT

Submission Date: March 20, 2000

Reviewer: Iftexhar Mahmood, Ph. D.

**Indication: Generalized Anxiety**

---

**Review of a Study Report**

**Title:** The pharmacokinetics and tolerability of buspirone during oral administration to children and adolescents diagnosed with an anxiety disorder (Protocol # CN101-123).

This was an open-label, non-randomized, single sequence, dose escalation study. Thirteen children ages 6 to 12, and 12 adolescents ages 13 to 17 years with anxiety disorder were enrolled in this study. The subjects received buspirone orally for three weeks and doses ranged from 10 to 60 mg daily. The subjects received 5 mg buspirone BID for 3 days, then dose was increased to 7.5 mg BID for 4 days. After this dose was found to be safe and tolerable, the subjects received 15 mg buspirone BID for 7 days during the second week. For the third week, the subjects received 30 mg BID for 7 days. Buspirone was available as 5 mg, 7.5 mg and 15 mg tablets. Blood samples (3 mL) were collected before dosing and at 1, 2, 4, 6, 8 and 12 hours after drug administration. Concentrations of buspirone and its metabolite, 1-pyrimidinylpiperazine (1-PP) were measured in plasma by \_\_\_\_\_

\_\_\_\_\_ The limit of detection for buspirone and 1-PP was \_\_\_\_\_, respectively. The pharmacokinetic parameters ( $C_{max}$ ,  $AUC(0-T)$  and  $T_{1/2}$ ) of buspirone and 1-PP in children were compared with the pharmacokinetic parameters obtained from a study conducted in 14 healthy subjects (8 men, 6 women) ages 18 to 45 years (Protocol # CN101-129). The dose and the dosing schedule of buspirone in adults were similar as those of children and adolescents.

The results of this study have been summarized in Tables 1-3. It should be noted that the reported  $AUC(0-T)$  is based on 8 hours sampling time as buspirone could not be detected in 12-hour blood samples in some

subjects. Furthermore, 5 mg buspirone dose was given to children and adolescents to evaluate whether or not they can tolerate this dose before receiving higher doses. Therefore, pharmacokinetics of 5 mg buspirone were not assessed in this group.

The results indicated that the  $C_{max}$  and AUC(0-T) of buspirone in children and adolescents at all doses were comparatively higher than the adults. The pharmacokinetics of 1-PP followed the same pattern as of buspirone. A comparison between children and adolescents indicated that the children had higher plasma levels of 1-PP than adolescents.

In children, mean buspirone  $C_{max}$  was 2.8, 2.5 and 1.6 times that of adults at the 7.5, 15 and 30 mg BID doses and the mean buspirone AUC(0-T) was 1.6, 1.7 and 1.1 times greater than adults. Adolescents also had higher mean buspirone  $C_{max}$  and AUC(0-T) than adults. The mean buspirone  $C_{max}$  was 2.9, 2.5 and 1.6 times that of adults at the 7.5, 15 and 30 mg BID doses. The mean buspirone AUC(0-T) was 2.0, 1.7 and 1.1 times greater in adolescents than that of adults at these doses. The  $C_{max}$  and AUC of buspirone were almost similar between children and adolescents.

Mean  $C_{max}$  and AUC(0-T) for 1-PP in children was approximately 2-fold higher than adults. In adolescents, the mean  $C_{max}$  of 1-PP was 25% higher than adults but AUC(0-T) was almost similar to the adults.

The half-lives of buspirone and 1-PP were comparable at all doses among all three groups.

**APPEARS THIS WAY  
ON ORIGINAL**

**TABLE 1**  
**Steady-state C<sub>max</sub> (ng/mL) of buspirone and 1-PP in children, adolescents**  
**and adults following multiple dosing**

Dose	Children	Adolescents	Adults	Ratio= ch/Adults	Ratio= Adol/adul	Ratio= ch/Adol
<b>Buspirone</b>						
7.5	0.88 ± 0.72	0.91 ± 1.03	0.31 ± 0.22	2.84	2.94	0.97
15	2.82 ± 3.07	2.86 ± 4.10	1.14 ± 0.64	2.47	2.51	0.99
30	4.78 ± 2.79	4.55 ± 4.89	2.94 ± 1.90	1.63	1.55	1.05
<b>1-PP</b>						
7.5	7.78 ± 4.38	4.38 ± 2.25	3.47 ± 1.74	2.24	1.26	1.78
15	14.19 ± 5.91	8.68 ± 4.02	7.19 ± 3.01	1.97	1.21	1.63
30	22.83 ± 5.62	17.12 ± 6.97	13.98 ± 6.08	1.63	1.22	1.33

**TABLE 2**  
**Steady-state AUC(0-T) (ng\*hr/mL) of buspirone and 1-PP**  
**in children, adolescents and adults**

Dose	Children	Adolescents	Adults	Ratio= ch/Adults	Ratio= Adol/adul	Ratio= ch/Adol
<b>Buspirone</b>						
7.5	1.97 ± 1.64	2.49 ± 2.53	1.24 ± 1.17	1.59	2.01	0.79
15	6.60 ± 6.53	6.75 ± 8.11	3.93 ± 2.02	1.68	1.72	0.98
30	11.98 ± 6.02	12.47 ± 12.34	11.47 ± 7.93	1.04	1.09	0.96
<b>1-PP</b>						
7.5	48.48 ± 37.78	25.53 ± 18.50	22.77 ± 14.63	2.13	1.12	1.90
15	86.99 ± 48.33	53.83 ± 32.14	49.78 ± 29.52	1.75	1.08	1.62
30	142.49 ± 43.46	99.11 ± 52.77	105.62 ± 59.33	1.35	0.94	1.44

**TABLE 3**  
**Steady-state half-life (hrs) of buspirone and 1-PP**  
**in children, adolescents and adults**

Dose	Children	Adolescents	Adults
<b>Buspirone</b>			
7.5	1.99 ± 0.92	2.90 ± 1.48	3.37 ± 0.78
15	3.13 ± 0.74	3.44 ± 1.29	3.51 ± 1.19
30	2.70 ± 0.88	3.38 ± 1.11	3.36 ± 1.10
<b>1-PP</b>			
7.5	4.47 ± 1.89	3.73 ± 1.26	4.21 ± 1.21
15	4.15 ± 1.09	4.33 ± 1.30	4.40 ± 1.42
30	3.88 ± 0.65	3.79 ± 0.98	4.65 ± 1.43

**Labeling Comments**

The Sponsor is requested to incorporate the following labeling changes. Please note that in the suggested labeling, change in fold is based on the arithmetic rather geometric mean.

At steady state, following doses of 7.5, 15, and 30 mg b.i.d., children (aged 6-12 years) had a mean buspirone  $C_{max}$  that was 2.8-fold, 2.5-fold, and 1.6-fold higher than that of adults, respectively. The mean buspirone AUC in children at these doses was 1.6-fold, 1.7-fold, and 1.1-fold higher, respectively. Across the dose range studied, the  $C_{max}$  and AUC of 1-PP in children were approximately twice than those of adults.

Adolescents (aged 13-17 years) had higher mean buspirone  $C_{max}$  and AUC(0-T) than adults. The mean buspirone  $C_{max}$  was 2.9, 2.5 and 1.6 times than that of adults at the 7.5, 15 and 30 mg BID doses. The mean buspirone AUC(0-T) was 2.0, 1.7 and 1.1 times greater in adolescents than that of adults at these doses. In adolescents, the mean  $C_{max}$  of 1-PP was 25% higher than adults but AUC(0-T) was almost similar to the adults.

The half-lives of buspirone and 1-PP were comparable at all doses among all three groups.

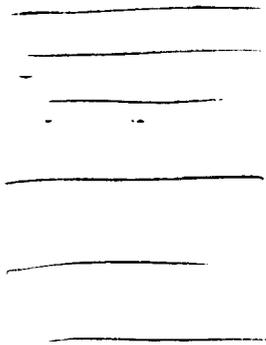
## Biowaiver Request

### Composition:

Bristol-Myers Squibb requests a waiver of in vivo bioequivalence between the buspirone hydrochloride (HCl) tablets used in the studies conducted in pediatric population (CN101-123, CN101-124, and CN101-125) and the 15 mg BuSpar<sup>R</sup> Dividose<sup>R</sup> tablets currently marketed. It should be noted that buspirone is not a narrow therapeutic range drug.

The buspirone tablets utilized in protocols CN101-123, CN101-124, and CN101-125 were 7.5 mg and 15 mg in strength. The 15 mg tablet was identical in composition to the currently marketed 15 mg BuSpar<sup>R</sup> Dividose<sup>R</sup> tablet, but was compressed without markings so that a blinded formulation could also be utilized in the studies to evaluate the safety and efficacy of buspirone in the pediatric population. Buspirone HCl tablets of 7.5 mg strength were manufactured utilizing the same excipients as the 15 mg tablets, but the amount of two of the ingredients were increased by a total of 7.5 mg so that the tablets would be the same weight and size as the 15 mg tablets, for the purpose of blinding. Thus, the drug:excipient ratio for the 7.5 mg and 15 mg tablets are different.

The composition of each tablet is provided in Table 1. There is currently no 7.5 mg BuSpar<sup>R</sup> marketed tablet. To prepare



Buspar 7.5 and 15 mg tablets are compositionally proportional with the marketed formulation with the exception of inactive ingredients, lactose and microcrystalline cellulose (SUPAC level I change, total change is less than 5%). These changes fall within the quantifiable range defined for compositional proportionality as per General BA/BE Guidance.

**Dissolution:**

Dissolution of buspirone HCl tablets was performed using the USP apparatus II at 50 rpm in a volume of 500 mL at  $37 \pm 0.5^{\circ}\text{C}$  in each of the following media taking multiple samples:

- (1) 0.1 N HCl, pH 1.0
- (2) acetate buffer, pH 4.5
- (3) phosphate buffer, pH 6.8.

The dissolution testing was performed on 12 dosage units for each of the following tablets for each medium:

- (1) buspirone HCl 7.5 mg tablet, Lot number: C98340, lot size 238,899 tablets
- (2) buspirone HCl 15 mg tablet, Lot number: C98341, lot size 239,551 tablets
- (3) buspirone HCl 15 mg Dividose<sup>R</sup> tablet, Lot number: 9G17391, lot size

The results are summarized in Table 3. For each tablet and medium, >90% of the labeled amount of buspirone HCl was dissolved by 30 minutes. The dissolution profiles were compared on the basis of the similarity factor ( $f_2$ ). The  $f_2$  values obtained are shown in Table 4. The results shown in Tables 3 and 4 indicate that the similarity factors are within recommended range of 50 to 100 for all comparisons, and greater than 85% of the labeled amount of buspirone HCl was dissolved in 30 minutes. These results demonstrate that buspirone HCl 7.5 mg and 15 mg tablets are rapidly dissolving and their dissolution profiles are similar to the marketed 15 mg BuSpar<sup>R</sup> Dividose<sup>R</sup> tablets.

Buspirone's dissolution specifications at the time of approval were as follows:

USP apparatus II at 50 rpm in 500 mL of 0.01 N HCl, pH 2.0.

Specifications: Not less than \_\_\_\_\_ % in 30 minutes. —

The Sponsor also compared the dissolution of 7.5 mg and 15 mg buspirone tablets with 15 mg buspirone Dividose<sup>R</sup> tablets at 30 minutes at pH 2.0. The results of this analysis suggested that at pH 2.0, the average % dissolved was \_\_\_\_\_, for 7.5 mg tablets and

94.1  for 15 mg tablets. Thus, 7.5 and 15 mg tablets meet the specification.

**Comments:**

1. The waiver request for in-vivo bioequivalence study for buspirone hydrochloride (HCl) tablets used in the studies conducted in pediatric population (7.5 and 15 mg tablets) can be granted based on:
  - (i) compositional proportionality and,
  - (ii) dissolution profiles, acceptable similarity factors and single time dissolution data.
2. The Sponsor is requested to adopt the currently established method and specification for these new strength of 7.5 mg and 15 mg tablets.

**Biopharmaceutics Classification System**

**Comment:**

3. The Sponsor has not provided detailed experimental information on the solubility of buspirone. The Sponsor is requested to provide this detailed information. The Sponsor is also requested to provide the detailed study report on permeability aspects of the drug which formed the basis of the journal articles (Metabolism and disposition of buspirone by Gammans et al, 1986 and Metabolism of the anti-anxiety drug buspirone in human subjects by Jajoo et al, 1989), so that the Agency can assess the permeability characteristics of the drug.

**Recommendations:**

The pharmacokinetic study report as submitted is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics provided the Sponsor incorporates the suggested labeling changes.

The detailed information on solubility and permeability is lacking as mentioned above. Therefore, at this time biowaiver can not be granted based on Biopharmaceutics Classification System. However, the Sponsor's bio-waiver request for in-vivo bioequivalence study for buspirone hydrochloride

(HCl) tablets used in the studies conducted in pediatric population (7.5 and 15 mg tablets) is granted based on compositional proportionality and dissolution data.

Please convey the labeling comments and comments 1-3 to the Sponsor.

Iftexhar Mahmood, Ph. D.  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph. D. \_\_\_\_\_

CC: NDA 18-731/S-043

HFD-120, HFD-860 (Mahmood, Baweja, Mehta), CDR-Biopharm (for Drug Files).

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 18-731/S-043

Bristol-Myers Squibb Company  
Attention: Michael S. Eison, Ph.D.  
Director, Regulatory Science  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Eison:

Please refer to your supplemental new drug application dated March 20, 2000, received March 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BuSpar® (buspirone hydrochloride) Tablets.

We acknowledge receipt of your submission dated April 3, 2001, which constituted a complete response to our January 18, 2001 action letter.

Further reference is made to the March 1, 2001, teleconference between FDA and Bristol-Myers Squibb regarding the proposed pediatric labeling for BuSpar® Tablets.

This supplemental new drug application provides for new language for pediatric use.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) which was approved on May 3, 2001, for S-045 and S-039 including the newly approved pediatric use language provided for in this supplement (S-043). Also included are the minor changes listed in your May 11, 2001, facsimile.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-731/S-043." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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

If you have any questions, call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 18-731/S-043

Bristol-Myers Squibb Company  
Attention: Michael S. Eison, Ph.D.  
Director, Regulatory Science  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Eison:

Please refer to your supplemental new drug application (NDA) dated March 20, 2000, received March 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BuSpar (buspirone hydrochloride) Tablets.

We also acknowledge receipt of your submission dated October 16, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling.

Since the data presented in this supplement do not support the efficacy of buspirone in the treatment of pediatric generalized anxiety disorder, we do not feel that it is appropriate to add statements to the labeling regarding this pediatric data other than under the 'Precautions-Pediatric Use' sections. We note that you have proposed labeling changes and additions to the 'Clinical Pharmacology', 'Precautions', 'Adverse Reactions', and 'Dosage and Administration' sections. However, given the negative study results, we believe that any labeling changes should be confined to the 'Precautions-Pediatric Use' sections.

**APPEARS THIS WAY  
ON ORIGINAL**

Thus, for the above reasons, your proposed labeling additions to the 'Clinical Pharmacology/Special Populations/Pediatric Patients', 'Clinical Pharmacology/Clinical Studies in Special Populations/Pediatric Clinical Experience', 'Adverse Reactions/Pediatric Clinical Experience', and 'Dosage and Administration/Pediatric Patients' should be omitted. We also ask you to adopt the following language under the 'Precautions/Pediatric Use' subsection:

*'The safety and effectiveness of buspirone were evaluated in two placebo-controlled six week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. When compared to placebo, there was no efficacy of buspirone on the symptoms of GAD in either study, using doses equal to those for adults (15-60 mg/day for up to six weeks). Pharmacokinetic studies have shown that, for identical doses, plasma exposures to buspirone and its active metabolite, 1-PP, are higher in pediatric patients than adults. Therefore, inadequate dosing is unlikely to be the explanation for the lack of effect in these trials. No unexpected safety findings were associated with buspirone in these studies. There are no long-term safety or efficacy data in this population.'*

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

/s/

-----  
Russell Katz  
1/18/01 05:15:17 PM

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 18-731

OCT 9 1998

Bristol-Myers Squibb Company  
Attention: Jay Gunther, Ph.D.  
5 Research Parkway  
Wallingford, CT 06492

Dear Dr. Gunther:

We acknowledge receipt on August 31, 1998, of your August 28, 1998, Proposed Pediatric Study Request for BuSpar<sup>R</sup> (buspirone HCl).

We have reviewed this proposal, and although it represents a useful starting point, we find that it does not adequately provide for what the Agency believes is the type of information needed. (You may wish to refer to your discussion of this subject with representatives of the Division of Neuropharmacologic Drug Products on June 25, 1998.) The Food and Drug Administration (FDA) is therefore providing a formal Written Request, pursuant to Section 505A(a) of the Federal Food, Drug, and Cosmetic Act, that you submit the following information which could support the safety and effectiveness of Buspar<sup>R</sup> Tablets in pediatric populations:

**Types of studies:**

Ordinarily a new claim for a drug must be supported by positive results from more than one adequate and well-controlled trial supporting the effectiveness of the drug for the entity in question. Under current law, it is possible to establish a claim in a pediatric population by either extrapolating from effectiveness results in adult studies for the same entity, or by relying on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder. Despite the fact that some experts in child psychiatry view generalized anxiety disorder (GAD) as essentially the same disorder in adults and children, a view that is legitimized to some extent by the inclusion of the GAD diagnosis for pediatric patients in DSM-IV, there remains some question regarding whether or not GAD can be considered the same disorder in adults and children. A major difficulty is that there is no experience from adequate and well-controlled trials of buspirone or, in fact, any other psychotropic agents in pediatric GAD upon which to draw any reassurance that this is a reasonable extrapolation. Consequently we believe it is necessary that an extension of the claim for buspirone in GAD into pediatric patients with this diagnosis be supported by positive results from two, independent, adequate and well-controlled clinical trials.

You have proposed an open label pharmacokinetic study (study 001) and an open label safety study (study 002). Although there is no objection to your conducting these studies, and although they may provide data complementing that obtained in the controlled trials, they are in themselves insufficient to provide meaningful clinical information for the treatment of the pediatric population with BuSpar<sup>®</sup>. We also suggest that population kinetic approaches applied to the controlled trials are more likely to elucidate relevant pharmacokinetic data and PK/PD relationships.

***Objective/rationale (for each study):***

The objective will be to determine the safety and efficacy of buspirone relative to placebo in the treatment of children and adolescents with GAD.

***Indication to be studied:*** Generalized anxiety disorder in children and adolescents

***Study design:***

The design of these studies should generally be similar to that of your proposed Study 003; i.e., randomized, double blind, placebo controlled, parallel group studies. At least one of the two studies should include treatment arms with two or more fixed doses of Buspar<sup>®</sup>. You may wish to consider dosages based upon the weight of the subject. The studies should be of sufficient duration to measure a meaningful clinical change in the disorder, i.e., several weeks.

***Age group in which studies will be performed:***

Your proposed age range of 6-17 is acceptable.

***Number of patients to be studied or power of study to be achieved:***

To be determined based on your choice of outcome measure.

***Entry criteria:***

The entry criteria should include a reliable and valid diagnostic method for identifying children and adolescents with GAD. As the diagnosis of GAD in this age group was established only a few years ago under DSM-IV, it would be desirable for you to provide the Agency with data supporting the validity of the chosen diagnostic method (such as the Kiddie-SADS suggested in your proposal). The entry criteria should also include a method for determining and handling comorbid diagnoses.

***Clinical endpoints/Outcome measures:***

The clinical endpoint chosen should be one that is expected to be sensitive to the effects of a drug on the symptoms of GAD. It should also be specific to the assessment of the manifestations of GAD and validated for that purpose.

**Study evaluations:** Study evaluations should include efficacy measurements and periodic safety assessments such as vital signs, weight, clinical laboratories, EKGs, and monitoring for adverse events. Additionally, it may be desirable to obtain pharmacokinetic blood samples; this would be of even more importance if you do not conduct a separate pediatric pharmacokinetic study.

**Drug information**

- *dosage form:* tablets
- *route of administration:* oral

**Safety concerns:** We are not aware of any unique safety concerns regarding Buspar<sup>R</sup> in the pediatric age group. However, any information relevant to the effect of Buspar<sup>R</sup> on the growth and development of children that derives from these trials would of course be meaningful.

**Statistical information:**

We have no specific requirements for the statistical analysis other than that it employ a valid methodology and that it be specified a priori in the protocol.

**Labeling that may result from the studies:**

Please note that the studies described herein address only the short term treatment of GAD in children and adolescents. Thus, any labeling that results from a positive finding of efficacy would apply to short term use. We would be happy to discuss the type of data that would be needed to address the issue of long term efficacy (i.e., relapse prevention).

**Format of reports to be submitted:** Full study reports or analyses not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

**Time frame for submitting reports of the studies:**

Reports of the above studies must be submitted to the Agency before May 14, 2008, to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request. If you would like to extend existing patent protection or exclusivity that expires before May 14, 2008, please submit reports of studies responsive to this Written Request at least 30 calendar days, not including the date of expiration, before the expiration of the existing patent protection or exclusivity you would like to have considered for extension.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. To avoid uncertainty, we recommend you seek a written agreement with FDA before developing pediatric studies. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

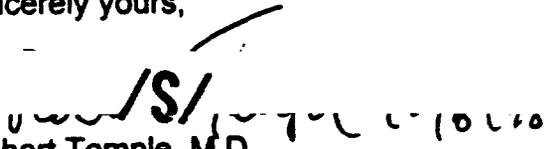
Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Ms. Anna M. Homonnay-Weikel, Project Manager, at (301) 594-5535.

Sincerely yours,

  
Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA

Division File

HFD-120/Leber/10.2.98

HFD-120/Laughren/10.1.98/10.2.98

HFD-120/Mosholder/10.1.98

HFD-120/Homonay

HFD-101/RTemple

HFD-600

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-6/KRoberts

*7/12 10-7-98 AM 10/7/98*

*AHW 10-7-98*

*10/8/98  
This version revised  
beyond the convention  
Suggested by the  
Office Director is  
acceptable to me  
/S/*

drafted: AHW/9.30.98

revised: AHW/10.2.98

final: AHW/10.2.98

revised: TL/10.7.98

final: AHW/10.7.98

**PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)**

**APPEARS THIS WAY  
ON ORIGINAL**

## MEETING MINUTES

Date: June 25, 1998

NDA: 18-731

Location: Woodmont II, Conference Room E

Firm: Bristol-Myers Squibb Company

Drug: BUSPAR (buspirone HCl) Tablets

Indication: childhood anxiety

### BMS Participants:

Anthony Santopolo, M.D.

Geoffrey Dunbar, M.D.

Carl Lewis, M.D., Ph.D.

Darlene Jody, M.D.

Neville Ford, M.D., Ph.D.

Donald Archibald, M.S.

Jay Gunther, Ph.D.

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### FDA Attendees:

Paul Leber, M.D.

Thomas Laughren, M.D.

Roberta Glass, M.D.

Andrew Mosholder, M.D.

Anna M. Homonnay-Weikel, R.Ph.

### BACKGROUND:

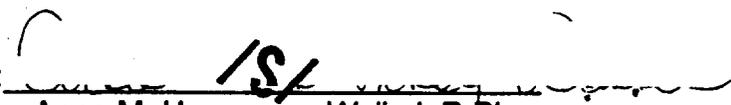
This meeting was requested by BMS to request the Division's guidance on their pediatric program for the treatment of anxiety in children, particularly as it relates to the pediatric exclusivity provisions of FDAMA. They have proposed one efficacy study supported by pharmacokinetic data and an open label safety study.

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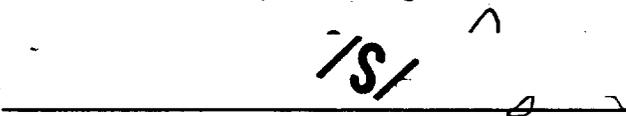
DISCUSSION:

- The Division has reservations about the diagnosis of generalized anxiety disorder (GAD) in children since the disease entity is not clearly established in children. If GAD could be established as an entity in children distinct from that in adults, then more than one controlled clinical trial would be needed to provide substantial evidence of efficacy in this population in order to grant a claim for this indication. It would be useful for the Division to have information on the natural course of this disease entity.
- BMS indicated that they may accept other labeling options as long as they could obtain the extended pediatric exclusivity available under the pediatric exclusivity provisions of FDAMA.
- In the absence of any guidance on the pediatric provisions of FDAMA, the Division could not offer any further comment.

Minutes prepared by:

  
Anna M. Homonnay-Weikel, R.Ph.  
Project Manager

Concurred by:

  
Thomas Laughren, M.D.  
Medical Teamleader PDP

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cc:

Orig NDA  
Div File  
HFD-120/PLeber  
HFD-120/TLaughren/9.3.98  
HFD-120/RGlass/9.2.98  
HFD-120/AMosholder/9.2.98  
HFD-120/AMHomonnay

MEETING MINUTES

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