MASSACHUSETTS INSTITUTE OF TECHNOLOGY

THE CLINICAL RESEARCH CENTER

Paul A. Spiers, Ph.D.
Visiting Scientist
508-887-6220

77 Massachusetts Ave, E17-438
Cambridge, MA 02139
617-253-6677

October 25th, 1995

Richard E. Gammans, Ph.D.,
Vice President, Clinical Development,
Interneuron Pharmaceuticals Incorporated,
99 Hayden Avenue, Suite 340,
Lexington, MA 02173.

Dear Dr. Gammans,

I recently completed my review of your report entitled *Evaluation of Clinical Data that pertains to the Human Risk for Adverse Neurologic, Psychiatric, Behavioral and Cognitive Effects of Dexfenfluramine.* The report covers an extensive literature including placebo-controlled, clinical trials and data from a decade of post-marketing surveillance in Europe. Most importantly, there is considerable data regarding those central nervous system functions which are most likely to be adversely effected by alterations in Serotonin metabolism.

Overall, the report makes it clear that Dexfenfluramine does not appear to pose any risk of neuropsychiatric or neurocognitive adverse effects. While it remains possible that the rare individual may experience some minor adverse reaction to this compound as a function of their unique metabolism or neurochemical constitution, Dexfenfluramine appears to be well tolerated, effective in achieving its stated purpose and very safe for consumption by the general public.

In conclusion, based on my review of the data, I would not hesitate to recommend to the FDA that it approve Dexfenfluramine for use in the United States as this drug does not, within the limits of my expertise, appear to pose any risk of adverse neuropsychological effects to the central nervous system.

Sincerely,

BEST POSSIBLE COPY

Paul A. Spiers, Ph.D.,
Clinical Psychologist / Neuropsychologist
Neuropsychology Associates, P.C.

Visiting Scientist, Clinical Research Center
Massachusetts Institute of Technology.

PAS/mac

Dr. A. John Rush

A. John Rush, M.D., holds the Betty Jo Hay Distinguished Chair in Mental Health, Department of Psychiatry, University of Texas Southwestern Medical Center in Dallas, Texas. He is a graduate of Princeton (B.A. Biochemistry, 1964); Columbia University College of Physicians and Surgeons (M.D., 1968); Northwestern University (Internship in Internal Medicine, 1969); and the University of Pennsylvania (Psychiatric Residency, 1972-75). He served in the U.S. Army (1969-71), and in the Special Action Office for Drug Abuse Prevention, Washington, D.C. (1971-72).

He is a Fellow of the American Psychiatric Association, the American College of Neuropsychopharmacology, and the American College of Psychiatry. He has served as President of the Society for Psychotherapy Research, Secretary-Treasurer of the Society of Biological Psychiatry, Chair of the DSM-IV Workgroup on Mood Disorders, and Chair of the Agency for Health Care Policy and Research Panel on Practice Guidelines for Depression. He has also served on three extramural NIMH Review Committees, the V.A. Merit Review Board, and presently chairs the NIMH Treatment Assessment Committee. He has published over 160 papers and book chapters, and six books.

For over 20 years, Dr. Rush has conducted clinical research that has spanned biological and psychosocial issues in mood disorders in adults, children and adolescents, and promoted the application of clinical research findings to improve the diagnosis and treatment for these patients. He has received the Strecker Award (Institute of Pennsylvania Hospital) and the Charles C. Burlingame Award (Institute of Living) in recognition of his research, teaching and clinical work. He is co-recipient of the Gerald L. Klerman Lifetime Research Award from the National Depressive and Manic Depressive Association. He is also the recipient of the Dallas Alliance for the Mentally Ill 1994 Professional of the Year Award.

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

A. John Rush, M.D.
Betty Jo Hay Distinguished Chair in Mental Health
Director, Mental Health Clinical Research Center

Department of Psychiatry
Kenneth Z. Altshuler, M.D
Chairman

October 26, 1995

Richard Gammans, .Ph.D.
Vice President, Clinical Research
Interneuron Pharmaceuticals, Inc.
99 Hayden Avenue, Suite 340
Lexington, MA 02173

Dear Dr. Gammans:

I am writing to summarize my review of the issue of the long-term safety of dex-fenfluramine (D-fenfluramine). I carefully read not only the reviews of the literature prepared by your staff, but quite a number of the original articles. The sum of my review is that at doses used in humans for the treatment of obesity, D-fenfluramine will have no long-term effects on CNS serotonin function (i.e., neurotoxicity).

The macaque monkey studies do show post-discontinuation CNS serotonin functional abnormalities, but there is no direct evidence of formally defined neurotoxicity. These findings in monkeys, however, are not generalizable to humans for the following reasons: (1) the doses are larger than therapeutic in some cases; (2) the metabolites generated by these animals are different than those made by humans; and (3) these animals differentially concentrate the drug and its metabolites in the CNS compared to humans.

Further evidence of long-term safety come from long-term on drug and post-discontinuation studies in humans in which psychiatric (e.g., depressive), neuropsychiatric (e.g., tests of information processing), and somatic/physiologic (e.g., appetite, weight control sleep disturbance) symptoms are not found with the drug. Most persuasive is the MRS study conducted on humans at therapeutic doses that reveals CNS concentrations of the drug that are not only quite low, but are at levels so minimal that gross 5HT concentrations are not changed.

The bottom line is that I could find no evidence of long-term neurotoxicity or neurofunctional impairment either on or off the drug in humans in therapeutic doses, nor animal studies that suggest such should be found. The long-term safety case for D-fenfluramine seems to be better established than with any new drug submitted for FDA approval.

Taken together with the medical morbidity and mortality of obesity, I would recommend this compound to any close relative, patient, or for myself, if the indication for treatment was present - given what we do know about long-term safety. I am sure the review committee will find the data quite persuasive of long-term safety as well.

Sincerely yours,

A. John Rush, M.D.

AJR/dls

Mental Health Clinical Research Center, St. Paul Professional Building I
5959 Harry Hines Blvd., Suite 600 / Dallas, Texas 75235 / (214)688-8321 Telefax (214)688-4278

Evaluation of Clinical Data that Pertain to the Human Risk of Adverse Neurologic, Psychometric, Behavioral and Cognitive Effects

October 26, 1995

Prepared by:

Richard E. Gammans, Ph.D.
Vice President, Clinical Development

ABSTRACT

A comprehensive medical and safety review of neurologic, psychometric, behavioral or cognitive data included in 17 controlled clinical trials, of 10 years of post-marketing spontaneous reports and of 55 reports in the published literature was conducted to evaluate the human risk for adverse psychologic, neurologic or psychiatric effects associated with dexfenfluramine (DF) treatment. The ratings were collected in therapeutic trials involving obese patients, or pilot therapeutic trials in other disorders, for the purpose of assessing the potential for adverse CNS consequences of DF treatment. These studies are substantial in terms of the number of patients investigated, the DF dose and duration of treatment, and the outcome measures employed. The neuropsychological tests and rating instruments used are well established in clinical neuropsychopharmacology and are capable of detecting clinically meaningful changes in response to drug exposure. Many of these same tests are recommended by WHO or NIMH for evaluating neurotoxicologic effects of human exposure to environmental or industrial chemicals. The review focused on human behaviors that serotonin is postulated to modulate (i.e., appetite, mood, suicidal ideation, attention, concentration, memory) or on neurologic signs.

Appetite is reduced by DF treatment, an effect consistent with its therapeutic effects. After abrupt discontinuation of DF following 3 months of treatment, structured assessment of food preferences in two studies at 1 month found no significant difference between DF-treated and placebo-treated patients, indicating that appetite returns to pre-treatment levels promptly. The weight loss response to DF 15 mg BID in patients who regained weight in the 2 months after discontinuing DF following 1 year of treatment (INDEX) compared to a group of placebo-treated patients was evaluated. Both groups had a similar response, indicating no lasting change in appetite resulting from 12 months of DF treatment.

Ten studies, including two studies with 3 months treatment and one month of post-treatment evaluation and three studies of 6 months duration, one of which (Noble Long-Term study) had a 12 month follow-up period, included well validated mood rating scales in addition to measures of appetite and weight. There were no differences between DF and placebo treatment on the mood scales, and there was no evidence of treatment emergent or post-treatment depression.

Ten studies, using sleep rating scales (e.g. Stanford Sleepiness Scale) including the 12 month INDEX study and the Noble Long-Term study (with 6 months treatment and 12 month follow-up), found no significant differences between DF and placebo in sleep quality. Mild daytime sedation was seen occasionally but resolved with continued treatment. No effects on sleep were observed post-treatment.

Three studies included various tests of attention, concentration, mental function, executive function and memory; no significant DF - placebo differences were observed. For example, the Noble Long-Term study, employing the Mini-Mental State Examination found no scores outside normal values and no DF - placebo differences either at the end of 6 months of treatment or during 12 months of post-treatment follow-up. These findings are in agreement with a published report that 32 weeks of fenfluramine plus phentermine treatment did not alter responses on the Memory Assessment Scales.

Three studies employed structured neurologic assessments and found no indication of adverse neurological signs with up to 3 months treatment and 1 month of post-treatment follow-up.

The results of this review indicate that at the clinical dose recommended for the treatment of obesity, dexfenfluramine is safe and well tolerated and is without risk of acute or delayed adverse effects involving the central nervous system. These findings are in concert with clinical experience comprised of over 10 million patient exposures that indicate a benign side effects profile and a favorable risk-benefit ratio for dexfenfluramine.

TABLE OF CONTENTS

GLOSSARY OF TEST ABBREVIATIONS AND DESCRIPTIONS

AAD — A self-report questionnaire used to quantify depressive symptoms associated with Seasonal Affective Disorder. (i.e., decreased energy, fatigue, social withdrawal, increased appetite, carbohydrate craving,, hypersomnia.)

BDI — Beck Depression Inventory - A self-rating 21-item instrument with 4-point rating scale to measure the depth of depression and to rapidly screen for depressed patients. Each item is concerned with a particular aspect of symptomatology and experience of depression i.e., Appetite, Work Inhibition, Mood, Sense of Failure, Indecisiveness.

CES-D — NIMH Center of Epidemiologic Studies-Depression - A self-report depression index questionnaire. It is a short scale designed to measure depressive symptomatology in the general population. It has high internal consistency, acceptable test-retest stability, concurrent validity by clinical and self-report criteria and substantial evidence of construct validity.

CFF — Critical Flicker Fusion - This is a test of perceptual integrity that determines at what rate a flashing, stroboscopic light is perceived by the subject as a steady source of illumination. This test was included in the original Halstead-Reitan Neuropsychological Battery.

CPT — Continuous Performance Test - A rapid detection of tachistoscopically presented digits that are interspersed among distractors; both digits and distractors are highly blurred. The test yields measures of perceptual sensitivity, response bias, and the decrement in performance during testing.

DE — Digit Elimination Test - In the digit elimination test, each subject is asked to cross out the digit 6 as many times as possible on a sheet where a high number of digits between 1 and 9, inclusive, are given in random order. Scoring is for errors (false positives) and number of targets crossed out. It is a useful assessment of visual scanning and activation and inhibition of rapid responses. It is also a test of attention, concentration, and speed.

DSST — Digit Symbol Substitution Test - In the digit symbol substitution test, a sample line is presented at the top of the page where each of the digits from 1 to 9 is paired with a simple geometric figure. The subject is required to fill in the correct figure under each digit. A large number of digits are displayed in random order below the sample line and the subject is asked to fill in as many items as possible in one minute. This is a test of fine motor speed, attention, concentration and self-regulation. DSST is consistently

more sensitive to brain damage than other Wechsler Intelligence Scales. Scores are likely to be depressed even when damage is minimal and to be among the most depressed when other tests are affected as well. The test is extremely sensitive to dementia, being one of the first tests to decline.

HAM-D — Hamilton Depression Rating Scale - A 17-item (or 23-item in Modified version) clinician-rated scale used to assess the severity of all symptoms that comprise a Major Depressive Episode. It includes evaluation of depressed mood, guilt, suicidality, motoric or psychic retardation, loss of interest in daily activity (anergia), psychic or somatic anxiety and sleep disturbance.

LC — Letter Cancellation - Test consists of rows of letters randomly interspersed with a designated letter. The patient is instructed to cross out all target letters in a specific time allotment. Scoring is for errors (false positives) and number of targets crossed out. It is a useful assessment of visual scanning and activation and inhibition of rapid responses. Lowered scores can reflect slowing and inattentiveness of diffuse damage or acute brain conditions.

MMS — Mini-Mental State Examination - A screening mental status examination made up of 5 subtests that assess orientation, attention, registration, recall and language. It tests a restricted set of cognitive functions, both simply and quickly. This formalized mental status assessment is one of the most widely used brief screening instruments for dementia. It is used either alone or with other evaluations.

NE — Neurologic Examination - A structured review of motor and sensory neurologic signs, each rated on a 5-point scale of severity. Assessment includes: muscle bulk, tone, muscle strength, deep tendon reflexes, coordination, balance, joint position, vibration, light touch and pin sensation.

POMS — Profile of Mood States - Patient-rated 5-point rating scale of 65 self-descriptive adjectives. Factors are constructed by grouping items to assess the following mood states: Depression/Dejection; Tension/Anxiety; Anger/Hostility; Confusion/Bewilderment; Vigor/Activity; Fatigue/Inertia. A Total Mood Disturbance Score is obtained by summing the scores across all six factors, weighing vigor/activity negatively. This is a relatively sensitive reactive measure of the subject's mood state. The POMS inventory has had its most extensive neuropsychological use with persons at risk for disorders due to toxic exposure. The POMS was incorporated into both the World Health Organization (WHO) core and full batteries, as

well as other batteries developed specifically for examining the effects of environmental and industrial toxins.

PRT — Pursuit Rotor Test - This is a test of visual tracking and sustained attention that requires the subject, who is seated in a dark room, to follow a moving luminous spot projected onto a wall. The subject must do this with a photosensitive pointer, held in the subject's hand, which also projects a spot of light. The subject must keep the spot of light projected from the pointer on top of the spot of light that is moving about the wall. The subject is scored on the amount of time the two lights are together. This test measures vigilance, fine motor control, reaction speed and concentration.

RT — Simple Auditory Reaction Time Performance - This test includes 125 trials of auditory stimulus presented after variable preparatory intervals of less than 3 seconds; subject releases telegraph key as rapidly as possible; test detects the acute emergence of concentration problems. Simple reaction time is frequently slowed with brain disease or injury.

SSS — Stanford Sleepiness Scale - Seven point self-rating scale that quantifies and determines the subject's level of alertness by rating it on a continuum of alertness to sleepiness.

VAMS — Visual Analogue Mood Scales - These scales typically involve a 100 mm horizontal line, the poles of which have words depicting the extremes of mood state. Scales used in the DF clinical trial include assessments of Lethargic, Satisfied, Tranquil, Lightheaded, Calm, Focused and Irritable states. VAM's have been shown to be reliable and valid measures of internal mood state in various populations.

INTRODUCTION

For over 20 years, interpretation of the observation that high doses of dexfenfluramine (DF) or fenfluramine markedly reduce forebrain serotonin concentration in animals has been debated. Regardless of how one might extrapolate these animal experimental findings to clinical use of DF, it is important to assess whether treatment of obese patients with DF poses an unacceptable risk for neurologic, behavioral, cognitive, or psychiatric adverse events or syndromes. The objective of this report is to review for safety the available neurologic, psychometric, behavioral and cognitive data from controlled trials in humans to determine if evidence exists of a clinical neurologic or psychiatric syndrome associated with DF treatment. No such evidence was found.

METHODS

Review Criteria

In the absence of a previously established clinical "serotonin neurotoxicity syndrome", the approach taken in this comprehensive review is to focus on those human behavioral, psychological or functional dimensions in which serotonin plays a modulatory role. The neurotransmitter serotonin has regulatory functions involving appetite; mood; suicidal ideation, suicide attempts or suicides; sleep; impulsive behavior; and attention, concentration or memory. In addition, the effects on neurologic function were also systematically evaluated in some studies and these data also have been carefully reviewed. Data that relate to each of these areas are summarized in this report. Finally a tabulated summary of each study is included in this review.

Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative that is a putative serotonin neurotoxin in animals. MDMA has been reported by some investigators to produce unique psychopathologic features in patients who abuse it. Some investigators have suggested that MDMA is a prototype serotonin neurotoxin and that psychopathology seen in MDMA abusers may represent the corollary human syndrome related to serotonin neurotoxicity. Chronic MDMA abusers exhibit symptoms of Substance Induced Psychoses (Diagnostic and Statistical Manual of Mental Disorders, 4th ed, 1994), also typical of amphetamine abusers. The unique features among MDMA abusers that are attributed to its effects on central serotoninergic function are depression, anxiety disorders, carbohydrate (and chocolate) craving, and memory disturbances (Krystal et al., 1992, Schifano & Magni, 1994). These descriptions derive from case reports involving less than 150 patients total. In the largest series of 100 patients, depression (21%) was the most prominent co-morbid feature (Peroutka, 1988). Therefore, symptoms reported among MDMA abusers were evaluated carefully in this safety review. It should be noted, however, that there is overwhelming evidence that DF is not a drug of abuse and does not share the dopaminergic effects of MDMA. Furthermore, no occurrence of depression following DF treatment has been found following systematic evaluations in placebo-controlled studies.

Sources of Data

Sixteen of the 44 clinical studies contained in NDA 20-344 (submitted May 1993) included control treatments and psychometric or neurologic assessments, as listed in Table 1. One additional placebo-controlled study by Noble that included a 12 month post-treatment follow-up period was completed in September, 1994, and was therefore not included in the NDA. Each of these 17 studies was carefully reviewed, and brief individual study summaries are provided.

The database of treatment-emergent adverse event reports was queried for self report adverse events (AE's) related to the dimensions of interest. In addition, a cluster of AE's was constructed to describe, using COSTART terms, possible syndromes indicative of neurotoxicity that might be overlooked by examining incidence rates of individual AE's. This cluster was comprised of the COSTART terms amnesia, confusion, depersonalization and thinking abnormal. The safety database was searched for patients reporting two or more of these symptoms at the same visit.

A second approach involved a literature search of over 900 publications of human data on DF or fenfluramine that identified 55 publications describing clinical investigations of DF or fenfluramine with psychological assessments. These published reports were also reviewed for indications of adverse findings.

Finally, as DF has been extensively marketed outside of the U.S. for more than 10 years, post-marketing spontaneous reporting of experiences were carefully reviewed. The estimated exposure to DF worldwide, from the number of capsules dispensed, is approximately 10 million individual patients.

TABLE 1: Controlled Clinical Studies with Neuropsychological Data[a]

Study	Study Type	Treatments	Outcome Measures
CP001	Single Dose	30,40,60 mg DF, 30 & 60 mg d,l-F, PBO	Vigilance, Mood, DSST, DE, Sleep
IP92-001	16 Days	30 mg q.d. then 15 mg BID	Neurological Exam
IP92-003	3 Months, 1 month follow-up	5,15, or 30 mg DF BID, PBO	Neurological Exam, HAM-D
IP92-005	3 Months, 1 month follow-up	15 mg BID, PBO	Neurological Exam, HAM-D
CP003	7 Days	15 mg BID, 30 mg d,l-F BID, PBO	DSST, DE, CFF, PRT, Sleep
CP004	8 Days	15 mg BID 30 mg q.d.	Sleep
MIT124	3 Months	15 mg BID, PBO	HAM-D
MIT296	3 Months	15 mg BID, PBO	POMS, SSS
VanItallie	3 Months, 3 month follow-up	15 mg BID, PBO	BDI
INDEX	1 Year	15 mg BID, PBO	Sleep
C010	3 Months	15 mg BID, PBO	Sleep, Food Intake Questionnaire, Activity, Mood
C003	3 Months	15 mg BID, PBO	Sleep
UK18	6 Months	15 mg q.d. x 1 week, 15 mg BID, PBO	POMS, VAMS
Noble Long-Term	6 Months, 12 month follow-up	15 mg BID, PBO	MMS, SSS, CES-D, POMS
MIT 237	1 Month	15 mg BID, PBO	HAM-D, AAD
MIT 251	Cross-over, three 16 day treatments	15 mg BID, PBO	HAM-D, Activity/Mood Questionnaire
MIT 291	5 Weeks	15 mg BID, PBO	POMS, RT, CPT, LC, DSST, SSS

[a]See glossary for test abbreviations and descriptions. See tabulated study summaries for details. PBO=placebo.

Expert Review Panel

The data summarized in this review were presented to independent experts who were asked to comment on the findings. The following individuals were included in this process:

Malcolm Lader, M.D., Ph.D.	Head, Clinical Psychopharmacology Unit (MRC) Professor of Psychiatry Institute of Psychiatry London, UK
A. John Rush, M.D.	Betty Jo Hay Distinguished Chair in Mental Health Professor of Psychiatry University of Texas Southwestern Medical Center and; Chairman, Mood Disorders Working Group American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
Ira Shoulson, M.D.	Louis Lasagna Professor of Experimental Therapeutics University of Rochester Medical Center and; Member, FDA Peripheral and Central Nervous System Advisory Committee
Paul A. Spiers, Ph.D.	Clinical Psychologist & Neuropsychologist Visiting Scientist, Clinical Research Center Massachusetts Institute of Technology Director, Neuropsychology Associates, PC

Brief biographical sketches and letters follow the tabulated study summaries; Dr. Shoulson's will be forwarded when available.

RESULTS

Appetite Control

A deficiency of serotonin may manifest itself by inducing an increased craving for food, especially carbohydrates. In fact, serotonergic brain lesions in animals produce hyperphagia. Food preferences have been examined in numerous clinical pharmacology studies that have consistently demonstrated a decrease in appetite among DF treated patients. In the most carefully controlled study, in which total food consumption was

monitored, carbohydrate craving was found to be reduced, suggesting an increase in synaptic serotonin brain levels.

Two large placebo-controlled studies (IP92-003 and IP92-005) involving over 400 DF-treated patients evaluated preference for sweet, starchy, protein, vegetable and fruit, and fatty foods during three months of DF treatment at doses from 15 mg to 30 mg BID and one month following abrupt discontinuation; approximately 300 of these patients received the recommended DF dose of 15 mg BID. As expected, there was a decreased preference for various foods during the three months of DF treatment.

Importantly, at one month following abrupt discontinuation of DF there were no differences between placebo and DF treatment (at any dose) in the change from baseline preference for carbohydrates or any other food type. These findings indicate that discontinuation of DF after prolonged treatment does not induce craving for carbohydrate, or any food type, after treatment at daily doses of up to 30 mg BID for 3 months.

Ditschuneit (1995) recently examined the weight loss effects of DF rechallenge in patients treated for 12 months with DF 15 mg BID (n=13) followed by 2 months off drug compared to a parallel group of placebo treated patients (n=12). The DF-treated patients regained 2.4 ± 0.5 kg during the 2 months off drug compared to 0.5 ± 0.2 kg for the placebo group. Both groups then were treated with DF 15 mg BID for 6 months. During this period, the patients who had received DF for 12 months previously lost 3.8 ± 0.6 kg compared to 4.6 ± 0.9 kg for the placebo group. These data indicate that weight loss response, and by inference appetite, is not altered by 1 year of DF 15 mg BID as compared to 1 year of placebo treatment. If DF treatment resulted in a significant deficit in CNS serotoninergic function, the weight loss response to DF rechallenge should be markedly attenuated. This was clearly not evident.

Taken collectively, these data indicate that DF treatment has no lasting effect on appetite and certainly does not produce hyperphagia. Patients who had 12 months of treatment remained responsive to the effects of DF upon rechallenge.

Mood Disorders and Depression

Evidence relating serotonin function to mood disturbance, especially Major Depression, is extant. A deficiency of serotonin neurotransmission is implicated in mood disorders. Therefore, emergence of depressive symptoms during DF treatment, or immediately following treatment discontinuation has been carefully reviewed. Five studies included periodic ratings during the course of DF treatment, and upon abrupt discontinuation, using the Hamilton Depression Rating Scale. One study included the Beck Depression Inventory. These scales quantify key dimensions of depressive disorders, (loss of motivation for daily activities i.e., depressed mood, sleep disturbance, guilt, suicidality, motor or psychic retardation, anergia). A total HAM-D score of $\geq$18 is typical in patients

with a Major Depressive Episode of at least moderate intensity. The findings for the three studies with the longest treatment duration, involving more than 400 DF-treated patients, are summarized in Table 2. No statistically significant difference in depressive symptomology between DF and placebo treatments was found either at the end of 3 months treatment or at 1 month after abrupt discontinuation of DF treatment. The mean scores for both placebo and treatment groups are low, in the normal range, and do not suggest the emergence of depressive symptoms in DF patients either during treatment at doses up to 60 mg/day for 12 weeks, or during the month following abrupt discontinuation.

TABLE 2: Depression Rating Scale Outcomes

		Mean Score (n)*		
Study and Scale	**Treatments**	**Baseline**	**Week 12**	**4 Weeks Post-Treatment**
IP92-003 (HAM-D)	PBO	3.5 (66)	3.2 (51)	2.7 (44)
	DF 5 mg BID	2.9 (67)	3.3 (52)	2.1 (44)
	DF 15 mg BID	3.6 (62)	3.7 (52)	2.2 (43)
	DF 30 mg BID	3.8 (69)	5.2 (54)	2.6 (41)
IP92-005 (HAM-D)	PBO	3.6 (168)	3.4 (116)	3.0 (110)
	DF 15 mg BID	3.6 (167)	3.5 (122)	2.6 (94)
Vanltallie (BDI)	PBO	5.3 (12)	4.6 (12)	Not tested
	DF 15 mg BID	6.9 (29)	5.5 (29)	Not Tested

*Mean Hamilton Depression (HAM-D) or Beck Depression (BDI) ratings; a score of $\geq$18 on either scale would be indicative of clinically important depression. Treatment group means for each study were not statistically significantly different using a repeated measures analysis of variance. Observed cases Least Squares means are presented in the table.

The other studies, MIT 124, MIT 251, MIT 237 and UK18, that measured mood had similar findings. The HAM-D findings in MIT 124 and MIT 251 also showed no significant increase in depressive symptoms on 3 months of treatment. In MIT 251, DF treatment prevented an increase, seen on placebo, in the depressive symptoms of premenstrual syndrome. In MIT 237, DF treatment resulted in a marked and statistically significant improvement in the depressive symptoms of Seasonal Affective Disorder, measured by HAM-D scores. In UK18 patients were significantly less depressed (POMS) on DF than placebo; there were no adverse changes on the VAMS.

To search for potential treatment effects on the core symptoms of depression, single symptom items of HAM-D were analyzed to identify individuals who experienced any

exacerbation of depressive symptoms. The patient data from the DF 15 mg BID group in studies IP92-003 and IP92-005 were pooled and compared to the pooled data from the corresponding placebo groups. For each symptom, the cohort of patients rated "mild" or "absent" at baseline on that symptom was selected, and those patients whose symptom worsened to a rating of "moderate" or "severe" on treatment were identified. A similar approach was applied to the post-treatment data for patients rated ≤ mild at the end of 12 weeks of DF treatment. These results are shown in Table 3. Neither the on-treatment nor post-treatment data show any evidence that DF causes adverse changes on depressive symptoms.

TABLE 3: Analysis of HAM-D Item Scores Among Patients from Studies IP92-003 or IP92-005 Treated with Dexfenfluramine 15 mg BID or Placebo

	Number of Patients Rated "Moderate" or "Severe" on Each Symptom (Number rated "Absent" or "Mild" at Baseline)			
	Treatment Week 12		4 Weeks Post-Treatment	
Symptom	PBO	DF	PBO	DF
Suicidal Ideation	0 (141)	0 (160)	0 (169)	0 (181)
Depressed Mood	0 (134)	0 (155)	0 (165)	1 (177)
Guilt	0 (140)	0 (157)	0 (167)	0 (178)
Psychic Anxiety	1 (131)	0 (144)	1 (161)	0 (166)
Somatic Anxiety	0 (137)	0 (154)	0 (164)	0 (179)
Retardation (Motor or psychic)	0 (141)	0 (158)	0 (168)	0 (179)
Loss of Interest in Daily Activity	0 (138)	0 (155)	0 (167)	0 (178)
Sleep Disturbance*	2 (131)	2 (158)	0 (151)	2 (173)

*sum of early, middle or late insomnia.

Another study, the Noble Long-Term Study, examined depressive symptoms for 12 months following six months of treatment with DF 15 mg BID using the NIMH Center for Epidemiologic Studies - Depression (CES-D) patient questionnaire (Table 4). There were no significant differences in mean depressive scores between the placebo and DF treatment groups at either end of treatment or after the 12-month follow-up. No patients receiving DF treatment for up to 6 months developed depressive symptoms, nor did the follow-up data indicate any post-treatment risk of emerging depression.

TABLE 4: On Treatment and Post-Treatment Depressive Symptom Scores from the Noble Long-Term Study

Treatment	NIMH Center for Epidemiologic Studies - Depression Scores[a]					
	Baseline	Time on Treatment		Follow-up (time since end of treatment)		
		3 Mo.	6 Mo.	3 Mo.	7 Mo.	12 Mo.
Placebo (n)	15 (28)	18 (26)	19 (23)	18 (15)	19 (16)	18 (21)
DF (n)	14 (26)	19 (26)	19 (25)	21 (22)	21 (17)	16 (19)

[a]No significant difference between treatment. Values are Least Squares means. A score of 35 is typical of patients with Major Depression.

In four studies the Profile of Mood States (POMS) self-rating scale was administered to evaluate the effect of DF on mood. The POMS is a patient-rated instrument that evaluates effects on six mood states: depression/dejection; anxiety/tension; anger/hostility; confusion/bewilderment; vigor/activity and fatigue/inertia. The POMS inventory has had its most extensive neuropsychological use in assessing risk for disorders of toxic exposure and was incorporated in the World Health Organizations core and full test batteries developed especially for examining effects of toxic exposure. The sensitivity of the POMS to effects of neurotoxins, or to medication effects, is well document (Lezak, 1995). The findings, summarized in Table 5, indicate that DF treatment does not adversely affect the mood dimensions tested by the POMS during up to 6 months of DF treatment or over a 12 month period following abrupt discontinuation.

TABLE 5: On Treatment and Post-Treatment POMS Factors Results

Study	BID Dose	N		Duration	POMS Factors
		PBO	DF		
Noble Long-Term	15 mg	26	26	6 Mo. Treatment 12 Mo. Followup	No difference from placebo
UK18	15 mg	20	22	6 Mo. Treatment	DF 6 month completers significantly less depressed; no other difference from placebo
MIT 296	15 mg	29	28	3 Mo. Treatment	DF significantly more fatigue at week 1, 6, 10 only; no other difference from placebo
MIT 291	15 mg	14	11	5 Wk. Treatment	No difference from placebo

Suicide and Impulse Control

Diminished central serotoninergic function is strongly implicated as a factor in suicide and suicide attempts. Blunted serotoninergic function, and especially lowered 5-HT_2 receptor function, is postulated to result in increased anger or hostility that is self-directed and may result in suicide or a suicide attempt. Data on the effects of DF on 5-HT_2 receptors in humans and on ratings of anger and hostility have been obtained. The strongest data to address suicidal behavior are, however, examination of the rate of suicide and suicide attempts in the post-marketing report data.

As 5-HT_2 receptor integrity is implicated in suicidal behaviors, the effects of DF on 5-HT_2 receptors in humans have been directly examined. Two placebo-controlled studies directly examined the effect of 3 months of DF treatment (15 mg BID) on 5-HT_2 receptors by Positron Emission Tomography (PET); each study employed a different, specific 5-HT_2 ligand (Baron and Guillon-Metz, 1995 and Lefebvre et al., 1995). One month following discontinuation of treatment, there were no treatment differences in indices of 5-HT_2 receptor binding.

Anger and hostility are evaluated in the POMS inventory. Four studies have shown no effect on the anger-hostility factor including one study with 6 months of DF treatment and a 12 month period following discontinuation. Tendency for impulsivity or impulsive behavior of the type that could lead to suicide or violent behavior was also evaluated by examination of the false-positive (i.e., impulsive) response rates of the DSST, LC or CPT tests in MIT 291. There was no significant treatment difference in the false-positive rate on these tests following 5 weeks of treatment with DF 15 mg BID compared to placebo; DF led to significantly fewer false-positive responses on the LC suggesting decreased impulsivity.

In the DF clinical trials involving over 3000 patients, there were no deaths due to suicide or impulsive acts. In 10 years of worldwide marketing there have been three deaths due to suicide and 60 suicide attempts (includes any suicide attempt and all intentional overdoses) in the post-marketing surveillance reports. Conservative estimates of suicide and attempted suicide rates (Table 6) based on these data are well below those for the general population in Western nations including the U.S. or those found for other drugs (Kapur et al., 1992). These results give no indication that DF treatment is associated with increased suicide or death from violent or impulsive action. On the contrary, the favorable findings of an apparent suicide rate that is only 10% of the population based estimate may merit independent investigation. The lack of increased risk of suicide, nevertheless, are consistent with the published report of Meyendorff et al., who found that d,l-fenfluramine significantly *reduced* ratings of suicidal behavior in suicidal patients, and with the present data showing absence of emergent suicidal ideation on the HAM-D (Table 3) in the clinical trials of DF.

TABLE 6: Post-Marketing Incidence of Suicide and Suicide Attempts

	Suicide	Suicide Attempts
DF[a]	0.3[b]/million patients	6/million patients
General Population[c]	198/million people	1980[a]/million people
Fluoxetine[d]	27/million patients	270[a]/million patients

[a]DF 10 million patients exposed
[b]Suicide attempts estimated at 10 times the suicide rate (Diekstra, 1993)
[c]Rate for 1986 adapted from Kapur et al., 1993
[d]FDA by Freedom of Information Act, Spontaneous Reporting System, Division of Epidemiology and Surveillance, February 1995

These data collectively give clear indication that DF treatment is not associated with increased suicidal behavior. This lack of increase in suicidal behaviors contradicts the hypothesis that DF treatment diminishes serotoninergic function.

Sleep

It has been postulated that diminished serotoninergic function might disrupt sleep control. Such disruptions might be manifested by insomnia reported in the context of a psychiatric disorder such as depression, as poor sleep quality, or as diminished cognitive function and daytime sleepiness secondary to poor quality of sleep. Effects of DF on sleep were assessed by various rating instruments in several studies, including the 12 month INDEX study and the Noble Long-Term study that included a 6 month treatment phase and a 12 month post-treatment follow-up. The results of sleep assessments in these studies are summarized in Table 7. From these data there is no evidence that DF treatment adversely affects sleep.

During the 19 placebo-controlled clinical weight-reduction studies, there was no significant difference between DF and placebo treatment in the number of spontaneous complaints of insomnia (19.9% DF vs. 18.6% PBO). When these various sleep ratings are examined, there are no findings indicating that DF treatment adversely affects sleep during up to 12 months of treatment. Taken collectively, these data indicate that DF treatment does not adversely affect sleep regulation.

TABLE 7: Sleep Assessment Outcomes in Placebo-Controlled Clinical Trials of DF

Study	BID Dose	Duration	Sleep Scale	Outcome
INDEX	15 mg	12 Mo Treatment	Sleepiness Questionnaire Time Slept	DF patients slept 12 min longer at month 2 only; no other treatment differences
Noble Long-Term	15 mg	6 Mo Treatment 12 Mo Follow-up	Stanford Sleepiness Scale	DF mildly sedating at 3 months; no difference on other treatment; no difference on follow-up
IP92-003	5,15,30 mg	3 Mo Treatment 1 Mo Follow-up	HAM-D Sleepiness Items	No difference on treatment or at follow-up
IP92-005	15 mg	3 Mo Treatment 1 Mo Follow-up	HAM-D Sleepiness Items	No difference on treatment or at follow-up
C003	15 mg	3 Mo Treatment	Sleep Questionnaire	No treatment difference
C010	15 mg	3 Mo Treatment	Sleep Questionnaire	No treatment difference
MIT 296	15 mg	3 Mo Treatment	Stanford Sleepiness Scale	DF patients sleepier at Week 1 only; no other treatment differences
MIT 291	15 mg	5 Weeks	Stanford Sleepiness Scale	No treatment difference
CP004	15 mg BID & 30 mg QD (cross-over)	8 Days Treatment	Stanford Sleepiness Scale	No treatment difference
CP003	DF 15 mg; d,lF 30 mg; (crossover)	7 Days Treatment	Stanford Sleepiness Scale	No treatment difference

Memory, Concentration or Mentation

Drugs acting on the CNS, including serotoninergic drugs, often have effects on mental functioning that can be reported as an Adverse Event (AE) under various COSTART terms. Table 8 compares the AE report findings from the placebo-controlled studies of DF 15 mg BID to that of four serotoninergic antidepressants for which data from placebo-controlled clinical trials are available. The incidence values from DF trials are similar, and often lower, than those seen with the other serotoninergic agents. The nine DF-treated (15 mg BID) patients (0.8%) who reported amnesia all regained normal memory function on continued treatment (4 patients) or after discontinuing DF treatment (5 patients). In IP92-003, four of 87 patients (4.6%) treated with 30 mg BID (2X higher than the recommended dose) reported, mild, intermittent memory disturbance, always with several

other side effects. All recovered completely within 1 to 3 weeks of discontinuing treatment. Also nine of 87 patients at the high dose reported decreased concentration, coded as "Thinking Abnormal." All patients recovered when treatment was discontinued. A dose of 30 mg BID is not generally recommended for treatment of obese patients due to the increased number of overall side effect incidences at this dose.

TABLE 8: Comparison of the Incidence (%) of Cognitive Function AEs for DF and Serotoninergic Drugs[a]

	Confusion	Amnesia	Thinking Abnormal
DF 15 mg BID (n=1159)	0.1	0.8	0.9
Fluoxetine (n=1178)	--[c]	0.4	0.5
Paroxetine (n=2963)	1.1	0.3	1.1
Nefazodone (n=3496)	2.0	1.5	1.6
Sertraline (n=1198)	--[c]	<1	0.6

[a]Incidence (%) derived from Summary Basis of Approval, FDA. Data shown are incidence in treated group minus the corresponding placebo incidence.
[b]Corresponds to patient complaint of lack of concentration, decreased alertness, transposing words or numbers, or abnormal ideation.
[c]COSTART term not used in this database.

In order to provide further assurance that DF does not cause a clinically troublesome decrease in mental function, the safety database was searched to identify any patient who experienced two or more of the following AE's concurrently: amnesia, confusion, or thinking abnormal. Only one patient, who reported intermittent memory decrease and confusion after 8 weeks of DF 15 mg BID, was identified in the database of >1100 patients. This patient complained of confusion and intermittent memory decrease; however, on memory testing, results were normal, the relationship to drug was judged to be remote, and no treatment or other intervention was required.

The above findings are in agreement with the recent publication of Greenberg et al. (1995). These investigators found that 32 weeks of phentermine plus fenfluramine treatment did not alter performance on the Memory Assessment Scale.

Psychometric and Cognitive Function Studies

Mental status was also monitored in the Noble Long-Term study using the Mini-Mental State Examination (MMS) during 6 months of DF treatment and 12 month post-treatment (Table 9). There are no significant differences between MMS means during placebo and DF treatment or in the post-treatment follow-up. No patient scored lower than 25 (out of

30) during or after treatment; a score of <20 is associated with clinically meaningful impairment of mental function.

TABLE 9: Noble Long-Term Study: Mini-Mental State Examination (Completers)[a]

	Baseline	Drug Treatment		12 Month Follow-up
		3 Months	6 Months	
Placebo (n=12)	28	29	29	29
DF (n=18)	28	28	29	29

[a]No significant difference between treatment groups was detected by Cochran-Mantel Haenszel Test on the observed-cases data set.

Effects of DF treatment on attention, concentration and mental performance were measured in three additional studies. Study MIT 291 was a parallel group, placebo-controlled 5 week study involving 24 obese female smokers who quit smoking receiving DF 15 mg BID (n=14) or placebo (n=11). Study CP003 was a crossover study comparing placebo, 15 mg DF BID and 30 mg d,l-fenfluramine BID, each administered for 7 days. CP001 was a single-dose, cross-over study comparing various doses of DF or fenfluramine. The testing battery in these studies included the Simple Auditory Reaction Time, Continuous Performance Test, Digit Symbol Substitution Test, Digit Elimination Test, Critical Flicker Fusion Test, Pursuit Rotor Test, and Letter Cancellation Test. There were no significant differences between treatment groups on any of these testing procedures (Table 10). These data indicate that up to five weeks of DF treatment (15 mg BID) did not result in diminished attention, concentration or cognitive function.

TABLE 10: Cognitive Function Test Results

Study	Design	Test	Outcome
MIT 291	Parallel Group, 15 mg DF BID vs. Placebo for 5 Weeks	Digit Symbol Substitution	No Treatment Difference*
		Letter Cancellation	No Treatment Difference*
		Simple Auditory Reaction Time	No Treatment Difference
CP003	Crossover 15 mg BID, 30 mg d,l-fenfluramine BID, Placebo	Digit Symbol Substitution	No Treatment Difference
		Digit Elimination	No Treatment Difference
		Critical Flicker Fusion	No Treatment Difference
		Pursuit Rotor	No Treatment Difference
CP001	Crossover 30, 40, 60 mg DF 30, 60 mg d,lF; Single Dose	Digit Elimination	No Treatment Difference
		Digit Substitution	No Treatment Difference

*False-positive responses, a separate outcome of this test, are discussed under impulsivity.

Published Reports

A comprehensive literature search revealed 55 publications of clinical trials of DF or d,l-fenfluramine that included psychological assessments as key index terms. Of these, 11 publications were controlled clinical studies that included psychometric, cognitive or psychopathologic assessment. These studies are briefly summarized in Table 11. None of the published clinical studies had findings indicative of adverse neuropsychologic effects associated with DF or d,l-fenfluramine treatment.

TABLE 11: Published Psychometric, Cognitive and Psychopathologic Controlled Studies[a]

Study	Study Type	Drug/Dose	Outcome
Baud P, Le Roch et al., 1989	Parallel group, single dose, 9 normal subjects/group	DF 15 mg, 30 mg, 60 mg, placebo	No significant psychometric effects
Fahy TA, Eisler I et al., 1993	Placebo-controlled, 8 week treatment; further 8 week follow-up; 43 bulimic patients	DF 45 mg/day	No differences in psychopathologic effects
Helem LA, de-Souza et al., 1993	Parallel group, single dose, 28 normal subjects	DF 30 mg, placebo	DF anxiety without affecting mentation
Aman MG, Kern RA et al., 1993	DB placebo, crossover; 28 children with attention deficit or mental retardation	F 15 mg/day	F superior to placebo on memory and attention
Grunberger J, Saletu B et al., 1993	Double-blind, placebo, crossover, single dose; 18 normal subjects	DF 15 mg, 30 mg, F 30 mg, placebo	No significant psychometric effects of DF, F
Stern LM, Walker MK et al., 1990	12 month, double-blind, crossover; 20 autistic children	F 1.5 mg/kg/day	Some improvement on F in cognition and language
Oades RD, Stern LM et al., 1990	5 month, double-blind, crossover; 7 autistic children	F 1.5 mg/kg/day	IQ and reaction time improved on F
Ekman G, Miranda-Linne et al., 1989	12 month, double-blind, placebo, crossover; 20 autistic children	F 1.5 mg/kg/day	No differences in effects on intellectual function
Blouin AG, Blouin JH et al., 1988	6 week, double-blind, placebo, crossover; 22 bulimic patients	F 60 mg/day, DMI 150 mg/day	Both F and DMI improved psychological & depressive symptoms
Ho HH, Lockitch G et al., 1986	Double-blind, placebo crossover; 7 autistic males	F 1.5 mg/kg/day	Slight improvement in short term memory, language skills on F
Bond AJ, Feizollah S, Lader MH, 1995	Single-dose, double-blind, placebo crossover; 12 normal subjects	DF 15 mg, 30 mg	Little psychometric impairment (slight effect on Episodic Memory)

[a]F=fenfluramine; DMI=desmethylimipramine

Neurologic Function

A structured neurologic examination, comprised of 10 items (muscle tone, strength, muscle bulk, deep tendon reflexes, coordination, joint position, vibration, light touch, pin sensation and balance) each rated as to severity, was used in three studies (IP92-001, IP92-003 and IP92-005). No DF, placebo differences were found on any of the functions examined.

SUMMARY

A comprehensive medical and safety review of neurologic, psychometric, behavioral or cognitive data included in 17 controlled clinical trials, of 10 years of post-marketing spontaneous reports and of 55 reports in the published literature was conducted to evaluate the human risk for adverse psychologic, neurologic or psychiatric effects associated with dexfenfluramine (DF) treatment. The ratings were collected in therapeutic trials involving obese patients, or pilot therapeutic trials in other disorders, for the purpose of assessing the potential for adverse CNS consequences of DF treatment. These studies are substantial in terms of the number of patients investigated, the DF dose and duration of treatment, and the outcome measures employed. The neuropsychological tests and rating instruments used are well established in clinical neuropsychopharmacology and are capable of detecting clinically meaningful changes in response to drug exposure. Many of these same tests are recommended by WHO or NIMH for evaluating neurotoxicologic effects of human exposure to environmental or industrial chemicals. The review focused on human behaviors that serotonin is postulated to modulate (i.e., appetite, mood, suicidal ideation, attention, concentration, memory) or on neurologic signs.

Appetite is reduced by DF treatment, an effect consistent with its therapeutic effects. After abrupt discontinuation of DF following 3 months of treatment, structured assessment of food preferences in two studies at 1 month found no significant difference between DF-treated and placebo-treated patients, indicating that appetite returns to pre-treatment levels promptly. The weight loss response to DF 15 mg BID in patients who regained weight in the 2 months after discontinuing DF following 1 year of treatment (INDEX) compared to a group of placebo-treated patients was evaluated. Both groups had a similar response, indicating no lasting change in appetite resulting from 12 months of DF treatment.

Ten studies, including two studies with 3 months treatment and one month of post-treatment evaluation and three studies of 6 months duration, one of which (Noble Long-Term study) had a 12 month follow-up period, included well validated mood rating scales in addition to measures of appetite and weight. There were no differences between DF and placebo treatment on the mood scales, and there was no evidence of treatment emergent or post-treatment depression.

Ten studies, using sleep rating scales (e.g. Stanford Sleepiness Scale) including the 12 month INDEX study and the Noble Long-Term study (with 6 months treatment and 12 month follow-up), found no significant differences between DF and placebo in sleep quality. Mild daytime sedation was seen occasionally but resolved with continued treatment. No effects on sleep were observed post-treatment.

Three studies included various tests of attention, concentration, mental function, executive function and memory; no significant DF - placebo differences were observed. For example, the Noble Long-Term study, employing the Mini-Mental State Examination found no scores outside normal values and no DF - placebo differences either at the end of 6 months of treatment or during 12 months of post-treatment follow-up. These findings are in agreement with a published report that 32 weeks of fenfluramine plus phentermine treatment did not alter responses on the Memory Assessment Scales.

Three studies employed structured neurologic assessments and found no indication of adverse neurological signs with up to 3 months treatment and 1 month of post-treatment follow-up.

The results of this review indicate that at the clinical dose recommended for the treatment of obesity, dexfenfluramine is safe and well tolerated and is without risk of acute or delayed adverse effects involving the central nervous system. These findings are in concert with clinical experience comprised of over 10 million patient exposures that indicate a benign side effects profile and a favorable risk-benefit ratio for dexfenfluramine.

REFERENCES

Aman M., Kern R., McGhee D., Arnold L. (1993): Fenfluramine and Methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: Laboratory effects. *J of Autism Dev Disor* 23:491-506.

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.

Baron and Guillon-Metz, Servier Study Report #C-5614-035-FRA

Baud P., Le Roch K., Sebban C. (1989): Effects EEG quantifies et psychometriques de 3 doses de dexfenfluramine chez l'adulte jeune. *Neurophysiol Clin* 19:241-55.

Blouin A., Blouin J., Perez E., Bushnik T., Zuro C., Mulder E. (1988). Treatment of bulimia with fenfluramine and desipramine. *J Clin Psychopharmacol* 8:261-9.

Bond A., Feizollah S., Lader M. (1995). The effects of D-fenfluramine on mood and performance, and on neuroendocrine indicators of 5-HT function. *J Psychopharm* 9:1-8.

Diekstra R. (1993). The epidemiology of suicide and parasuicide. *Acta Psychiatr Scand* (Suppl 371):9-20.

Ditschuneit H., Flechtner-Mors M., Alder G. (1995). Dexfenfluramine in the treatment of obesity. *Obesity Research* 3(suppl.3) 355s, O-121.

Ekman G., Miranda-Linne F., Gillberg C., Garle M., Wetterberg L. (1989). Fenfluramine treatment of twenty children with autism. *J Autism Dev Disord* 19:511-32.

Fahy T., Eisler I., Russell G. (1993): A placebo-controlled trial of d-fenfluramine in bulimia nervosa. *Br J Psychiatry* 162:597-603.

Greenberg I., Blank R., Schumacher G., Blackburn G., Borrazzo E. (1995) Short term memory and the use of combination low dose phenteramine and fenfluramine. *Obesity Research* 3(suppl.3) 355s, O-123.

Grunberger J., Saletu B., Linzmayer L., Barbanoj M. (1993). Clinical-pharmacological study with the two isomers (d-,l-) of fenfluramine and its comparison with chlorpromazine and d-amphetamine: Psychometric and psychophysiological evaluation. *Meth Find Exp Clin Pharmacol* 15:313-328.

Hetem L., de-Souza C., Guimaraes F., Zuardi A., Graeff F. (1993): D-fenfluramine reduces anxiety induced by simulated public speaking. *Brazilian J Med Biol Res* 26:971-974.

Krystal J., Price L., Opsahl C., Ricaurte G., Heninger G. (1992). Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: Effects on mood and neuropsychological function? *Am J Drug Alcohol Abuse* 18:331-341.

Ho H., Lockitch G., Eaves L., Jacobson B. (1986). Blood serotonin concentrations and Fenfluramine therapy in autistic children. *J Pediatr* 108(3):465-9.

Lefebvre, Franck and Comar, Servier Study Report #C-5614-037-BEL

Lezak M.D. *Neuropsychological Assessment*, Third Edition. New York, New York: Oxford University Press, Inc. 1995.

Oades R., Stern L., Walker M., Clark C., Kapoor V. (1990). Event-related potentials and monoamines in autistic children on a clinical trial of fenfluramine. *Int J Psychophysiol* 8:197-212.

Peroutka S., Newman H., Harris H. (1988). Subjective effects of 3,4-methylenedioxymethylamphetamine in recreational users. *Neurospychopharmacology* 1:283-287.

Schifano F., Magni G. (1994). MDMA ("Ecstasy") Abuse: psychopathological features and craving for chocolate: A case series. *Biol Psychiatry* 136:763-767.

Stern L., Walker M., Sawyer M., Oades R., Badcock N., Spence J. (1990). A controlled crossover trial of fenfluramine in autism. *J Child Psychol Psychiatry* 31:569-85.

TABULATED INDIVIDUAL STUDY SUMMARIES

"The Study of the Activity and Acceptability of Several Doses of Dexfenfluramine After Single Dose Administration to Healthy Volunteers: Double Blind Comparison with *d,l*-Fenfluramine and Placebo" (Study Number CP5614 34 001, NDA No. 20-344, Volume 75, page 161)

Principal Investigators: Dr. Paul Turner and Dr. Trevor Silverstone

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL, NEUROLOGICAL & COGNITIVE MEASURES	STUDY RESULTS
CP001	16 non-obese subjects	PBO 30mg DF 40mg DF 60mg DF 30mg d,l-F 60mg d,l-F **TREATMENT DURATION** each dose X 1 day	single-center, randomized, double-blind, placebo-controlled, crossover group trial with screening phase and 6 treatment periods; each treatment period was 7 days with 1 day of single dosing treatment followed by 6 days washout period before next treatment period; testing was performed on each dosing day of treatment at designated hours	1. Vigilance Rating Scale* 2. Mood Rating Scale* *100mm linear rating scales at hours 0, 1, 2, 3, 4, 5, 6, 7 and 8 3. Digit Symbol Substitution Test at hours 0, 3.5, 5.5 and 7.5 4. Digit Elimination Test at hours 0, 3.5, 5.5 and 7.5 5. Sleep Rating Scale** a. quality b. falling asleep c. awakenings d. time of awakening **100mm linear rating scales at hour 24	1. No significant difference between treatment groups 2. No significant difference between treatment groups 3. Performance at hour 3.5 on 60 mg DF was significantly ($p < 0.01$) lower compared to all other treatments at same time point and remained significantly lower at hour 5.5 ($p < 0.05$) compared to placebo and 30mg d,l-F 4. No significant difference between treatment groups 5a. Significant difference ($p < 0.05$) between 60 mg DF & 30 mg d,l-F with 60 mg DF showing poorest sleep b. Significant difference ($p < 0.01$) in pairwise comparisons between 60 mg DF & 30 mg of both DF and d,l-F with more difficulty in 60 mg DF c. No significant difference between treatment groups d. No significant difference between treatment groups

"Single-Dose and Steady State Pharmacokinetics of Dexfenfluramine in Obese Patients and Healthy, Non-Obese Subjects" (Study Number IP92-001, **NDA No. 20-344, Volume 75, page 003)**

Principal Investigators: Dr. Monte L. Scheinbaum and Dr. Ramon Vargus

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
P001	Random. n=56 29 obese 29 non-obese Completers n=48 12 obese males 12 obese females 12 non-obese males 12 non-obese females (age-matched ± 5 years)	1. Initial single oral 30 mg DF dose 2. Four days later, 15 mg DF BID (every 12 hours) X 14 days 3. On the following day, 15 mg DF, 12 hours apart X two doses **TREATMENT DURATION** Total 16 days over 28 day period	single-center, single- and multiple-dose periods, unblinded parallel design. Each subject received inital single oral dose (1) + 5 days inpatient sampling. After a 4 day washout period (outpatient), subjects self-administered med (2) for 14 days, then received two oral doses (3) for 1 day (outpatient) + 5 days sampling.	1. Neurological Assessment at screening and day after last dosing day Motor Examination: a. muscle bulk b. tone c. muscle strength d. deep tendon reflexes e. coordination f. balance Sensory Examination: a. joint position b. vibration c. light touch d. pin sensation	1. No significant difference between baseline and treatment examinations

"Placebo-Controlled, Dose-Response Study of Dexfenfluramine in the Management of Exogenous Obesity" (Study Number IP92-003, NDA No. 20-344, Volume 103, page 228)

Principal Investigators: Multicenter

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL, NEUROLOGICAL & COGNITIVE MEASURES	STUDY RESULTS
P003	obese patients Random. PBO=85 10mg=85 30mg=82 60mg=87 Completers PBO=57 10mg=56 30mg=58 60mg=54	PBO, 5, 15, or 30 mg DF BID **TREATMENT DURATION** 12 weeks	multicenter, randomized, double-blind, placebo-controlled parallel group trial with 2 week screening/ placebo run-in period followed by a 12 week treatment period and 4 week post-treatment follow-up period *patients were screened psychologically healthy as defined by DSM-IIIR	1. Neurological Assessment at weeks -2, 12 and 16 Motor Examination: a. muscle bulk b. tone c. muscle strength d. deep tendon reflexes e. coordination f. balance Sensory Examination: a. joint position b. vibration c. light touch d. pin sensation 2. Hamilton Depression Scale Rating at weeks 0, 12, 14 and 16	1. No significant difference among treatment groups were observed at screening, termination or post-treatment 2. There were no statistically significant differences among treatment groups in total Hamilton Depression Scale ratings, or the change from baseline ratings. No evidence of depression as a withdrawal symptom was observed.

"A Placebo-Controlled Study of Dexfenfluramine in the Management of Exogenous Obesity" (Study Number IP92-005, NDA No. 20-34, Amendment #2, Volume 3, page 112)

Principal Investigators: Multicenter

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL, NEUROLOGICAL & COGNITIVE MEASURES	STUDY RESULTS
P005	obese patients* Random. PBO=169 DF=168 Completers PBO=108 DF=116 *patients were screened psycho-logically healthy as defined by DSM-IIIR	PBO or 15 mg DF BID TREATMENT DURATION 12 weeks	multicenter, randomized, double-blind, placebo-controlled parallel trial with 2 week screening/ placebo run-in period followed by a 12 week treatment period and 4 week post-treatment follow-up period	1. Neurological Assessment at weeks -2, 12 and 16 Motor Examination: a. muscle bulk b. tone c. muscle strength d. deep tendon reflexes e. coordination f. balance Sensory Examination: a. joint position b. vibration c. light touch d. pin sensation 2. Hamilton Depression Scale Rating at weeks 0, 12, 14 and 16	1. No significant difference between treatments; all patients neurologically normal. No post-treatment withdrawal emergent effects. 2. There were no statistically significant differences seen between treatment groups or compared to baseline in total HAM-D Scale scores at the week 12 or post-treatment evaluations. No evidence of depression as a withdrawal symptom was observed.

"The Effect of 30 mg Dexfenfluramine on General Behavior, Sleep and Eating Behavior After Administration to Obese Patients for Seven Days: A Double-Blind Comparison with 60 mg *d,l*-Fenfluramine and Placebo" (Study Number CP 5614 34 003, NDA No. 20-344, Volume 79, page 171)

Principal Investigators: Dr. Paul Turner and Dr. Trevor Silverstone

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
CP003	12 obese patients	PBO 15 mg DF BID 30 mg d,l-F BID **TREATMENT DURATION** administration for 7 days	single center, randomized, double-blind, crossover study with screening phase and 3 treatment periods; each treatment phase was 7 days in duration followed by a 7 day washout period between treatments	1. Digit Symbol Substitution Test* 2. Digit Elimination Test* 3. Critical Flicker Fusion Test* 4. Pursuit Rotor Test* *Baseline day of each treatment period (Day 0), and on follow-up day of each post-treatment period (Day 8) 5. Quality of sleep (5-point scale)** 6. Difficulty falling asleep (3-point scale)** 7. Sleep interruption (3-point scale)** 8. Awakening earlier than usual (2-point scale)** **Treatment Days 1-7	1. No significant difference between treatment groups 2. No significant difference between treatment groups 3. No significant difference between treatment groups 4. No significant difference between treatment groups 5. No significant difference between treatment groups 6. No significant difference between treatment groups 7. No significant difference between treatment groups 8. No significant difference between treatment group.

"A Comparative Study of the Acceptability of Dexfenfluramine at a Daily Dosage of 30 mg Administered in One or Two Daily Doses to Healthy Volunteers" (Study Number CP 5614 34 004, **NDA No. 20-344, Volume 80, page 161)**
Principal Investigator: Dr. Trevor Silverstone

STUDY	#	DOSE	STUDY DESIGN	BEHAVIORAL, NEUROLOGICAL & COGNITIVE MEASURES	STUDY RESULTS
CP004	10 non-obese subjects	15 mg DF BID 30mg DF QD **TREATMENT DURATION** administration for 8 days	single-center, randomized, double-blind, crossover study designed to compare the effects of 30 mg DF given orally qd versus 15 mg DF BID. Study consisted of a screening phase and two dosing periods. During dosing periods, subjects were hospitalized on Day 1 and 8 of each treatment. Six-day washout periods separated each dosing phase.	1. Quality of sleep (3-point scale) on mornings of Day 2 through Day 8	1. No significant difference between treatment regimens

"Effect of Prolonged Treatment with Dexfenfluramine on Consumption of Carbohydrate Snacks by Overweight Subjects Who Do and Do not Exhibit Carbohydrate-Craving" (Study Number MIT 124, **NDA No. 20-344, Volume 89, page 002**)
Principal Investigator: Dr. Judith Wurtman

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
MIT 124	obese subjects <u>Random</u> PBO=40 DF=40 <u>Completers</u> PBO=38 DF=32	PBO or 15 mg DF BID **TREATMENT DURATION** 12 weeks	single-center, randomized, double-blind, parallel group study designed to compare the effects of 15 mg DF administered BID versus PBO. Study consisted of screening phase and 12 week dosing periods followed by a post-treatment phase.	1. Hamilton Depression Scale (Modified) at weeks 0 and 12	1. No significant difference between treatment groups

"The Effect of Dexfenfluramine and Fluoxetine on Weight Loss Among Female Obese Carbohydrate Cravers" (Study Number MIT 296, NDA No. 20-344, Volume 94, page 001)

Principal Investigator: Dr. Judith Wurtman

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
MIT 296	obese female subjects <u>Random.</u> PBO=29 DF=28 FL=30 <u>Completers</u> PBO=25 DF=21 FL=18	1. PBO TID 2. 15 mg DF BID and PBO QD, or 3. 20 mg fluoxetine TID *Subjects received identical packets of three pills and were told to take one pill TID **TREATMENT DURATION** 12 weeks	single-center, randomized, double-blind, parallel group study designed to compare the effects of 15 mg DF administered BID (with midday PBO) versus fluoxetine 20 mg TID, versus PBO TID. Study consisted of screening phase and baseline period of 5 days, followed by a 12 week dosing period.	1. Profile of Mood States at baseline and weeks 1-12 a. Tension/Anxiety Score b. Depression/Dejection Score c. Anger/Hostility Score d. Vigor/Activity Score e. Fatigue/Inertia Score f. Confusion/Bewilderment Score g. POMS Mood Disturbance Score 2. Stanford Sleepiness Scale at baseline and weeks 1-12	a. No significant difference b. No significant difference c. No significant difference d. No significant difference e. DF patients had significantly higher mean fatigue scores at weeks 1, 6, and 10 ($p \leq 0.05$), and higher mean fatigue scores than PBO patients at almost all time points. Similarly, fluoxetine patients had higher mean fatigue scores at almost all time points compared PBO patients, although results were not statistically significant. POMS-Fatigue results are consistent with the generally higher frequency of asthenia reported as an adverse event by DF and fluoxetine patients as compared to PBO patients, with overall difference in rate approaching statistical significance, Cochran-Mantel-Haenszel test of Incidence, p= 0.068 (DF 14/28, 50.0%; F 15/30, 50.0%; PBO 7/29, 24.1%) f. No significant difference g. No significant difference 2. DF patients were significantly ($p < 0.01$) sleepier than PBO at week 1 only and F at weeks 1 and 10 only ($p < 0.05$); no other significant differences were noted between treatments

"Therapeutic Benefit of Dexfenfluramine on Body Composition and Weight Loss After Three Months of Treatment in Obese Outpatients" (Study Identification Van Itallie Study, **NDA No. 20-344, Volume 146, page 002)**
Principal Investigators: Dr. Theodore Van Itallie and Dr. Steven Heymsfield

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
Van Itallie Study	obese patients <u>Random</u> PBO=29 DF=57 <u>Completers</u> PBO=12 DF=29	PBO or 15 mg DF BID **TREATMENT DURATION** 12 weeks	single center, randomized, double-blind, placebo-controlled, parallel group trial with baseline phase of 7 days and 12 week treatment period, followed by a 3 month follow-up period	1. Beck Depression Inventory at -1 week and month 3	1. No significant difference between treatment groups

"An International Multicenter Study: Efficacy and Safety of Long-Term Administration of Dexfenfluramine in Obese Patients"
(Study Identification INDEX, NDA No. 20-344, Volume 154, page 045)
Principal Investigators: Multicenter

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
INDEX Study	obese patients Random. PBO=527 DF=518 Completers PBO=280 DF=311	PBO or 15 mg DF BID TREATMENT DURATION 12 months	multinational (9 country), 24 center, randomized, double-blind, placebo-controlled, parallel group, 12 month trial was designed to compare the effects of administering DF with PBO. A one to 15 day pre-treatment period was followed by a 12 month treatment period and 2 month follow-up period	1. Sleep Rating Scale at month 0, 1, 2, 4, 6, 8, 10, 12 a. quality b. hours of sleep c. falling asleep d. difficulty in waking up	 a. No significant difference between treatment groups b. Statistically significant difference between groups at month 2 with mean change + 0.2 hours (12 minutes) in DF group and no change in PBO group c. No significant difference between treatment groups d. No significant difference between treatment groups

"Study to Investigate the Efficacy and Safety of Dexfenfluramine in the Treatment of Obesity in a Three-Month, Double-Blind, Placebo-Controlled Study" (Study Number C 5614 34 010, **NDA No. 20-344, Volume 240, page 002)**
Principal Investigator: Dr. J. W. H. Doar

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
C010	obese patients <u>Random</u>. PBO=34 DF=40 <u>Completers</u> PBO=28 DF=34	PBO or 15 mg DF BID **TREATMENT DURATION** 12 weeks	single center, randomized, double-blind, placebo-controlled, parallel group trial, designed to compare the effects of administering 15 mg DF BID with PBO	1. Sleep Assessment (3 point rating scale)* a. quality of sleep b. change in sleep 2. Food Intake Questionnaire (3 point rating scale)* 3. Behavior - Activity (3 point rating scale)* 4. Behavior - Mood (3 point rating scale)* *Weeks -1, 0, 2, 4, 6, 8, 10 and 12	 a. No significant difference between treatment groups b. A greater percentage of DF patients reported no change in their sleep compared to placebo 2. No significant difference between treatment groups 3. No significant difference between treatment groups 4. No significant difference between treatment groups

"The Efficacy and Acceptability of 30 mg Dexfenfluramine Administered Daily for Three Months to Patients with Refractory Obesity: A Double-Blind Placebo-Controlled Study" (Study Number C 5614 34 003, **NDA No. 20-344, Volume 248, page 002**)
Principal Investigators: Dr. Harry Keen and Dr. Nick Finer

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
C003	obese patients Random. PBO = 20 DF = 19 Completers PBO=19 DF=17	PBO or 15 mg DF BID **TREATMENT DURATION** 12 weeks	single center, randomized, double-blind, placebo-controlled, parallel group trial, designed to compare the effects of administering DF with PBO; study consists of 2 phases, the Screening/ Baseline (Run-in) Phase and the Treatment Phase of 12 weeks	1. Subjective Sleep Assessment at months 0, 1, 2 and 3	1. Improvement in quality of sleep from baseline in DF-treated patients; treatment by month interaction, p = 0.02

"Dexfenfluramine and Weight-Maintenance After Very Low Calorie Liquid Diets" (Study Number C 5614 18 UK, NDA No. 20-344, Volume 269, page 201)

Principal Investigators: Dr. Nick Finer and Dr. Harry Keen

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
UK18	obese patients Random. PBO = 22 DF = 23 Completers PBO = 16 DF = 16	1 capsule of either 15 mg DF or placebo every A.M. for the first week of treatment, and then 15 mg DF or PBO BID **TREATMENT DURATION** 26 weeks total treatment	single center, randomized, double-blind, placebo-controlled, parallel group trial designed to examine the effects of DF administered to severely obese patients for 26 weeks after an 8 week very low calorie diet.	1. Profile of Mood States at weeks -8, -6, -4, -2, 0, 2, 6, 10, 14, 18, 22 and 26 a. Tension/Anxiety Score b. Depression/Dejection Score c. Anger/Hostility Score d. Vigor/Activity Score e. Fatigue/Inertia Score f. Confusion/Bewilderment Score g. POMS Mood Disturbance Score 2. Visual Analogue Mood Scale at weeks -8, -6, -4, -2, 0, 2, 6, 10, 14, 18, 22 and 26 a. Lethargic b. Satisfied c. Tranquil d. Lightheaded e. Calm f. Focused g. Irritable	1. DF group showed significantly less depression ($p < 0.05$) compared to the PBO group at 6 months (week 26). No significant differences otherwise between treatment groups in any POMS factor or in the total POMS Mood Disturbance scores 2a - g. No significant difference between treatment groups in any one category of the VAMS

"Effects of Dexfenfluramine (15 mg, BID, po) on Cognitive Function in Obese Patients: A Double-Blind, Randomized, Parallel, Placebo-Controlled, Long Term Study Over 18 Months" (Study Number CL2-5614-USA, **NDA No. 20-344, Amendment #28**)
Principal Investigator: Dr. Rudy Noble

STUDY	#	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
CL2-5614-USA (Noble Long-Term Study)	obese patients Random. PBO=35 DF=36 Treatment Completers PBO=21 DF=24 Post-Treatment Follow-up PBO=22 DF= 20	PBO or 15 mg DF BID TREATMENT DURATION 6 months	single center, randomized, double-blind, placebo-controlled, parallel group trial, designed to compare the effects of administering DF with PBO for 6 months and 12 month single-blind placebo follow-up period (total study duration = 18 months)	1. Mini Mental State Examination†* 2. Stanford Sleepiness Scale* 3. Center for Epidemiologic Studies Depression Scale* 4. Profile of Mood States* a. Tension/Anxiety Score b. Depression/Dejection Score c. Anger/Hostility Score d. Vigor/Activity Score e. Fatigue/Inertia Score f. Confusion/Bewilderment Score g. POMS Mood Disturbance Score *All assessments at week -1 and months 3, 6, 9, 13 and 18	1. No significant difference between treatment groups 2. At month 3, DF group had significantly more reports of mild sedation ("a little foggy/not at peak") than PBO ($p < 0.03$). By the end of treatment, month 6 and post-treatment follow-up, months 9, 13, and 18, there were no significant differences between treatment groups 3. No significant difference between treatment groups 4a - g. No significant difference between treatment groups in any POMS factor or in the total POMS Mood Disturbance scores

"Seasonal Affective Disorder and Carbohydrate Craving" (Study Number MIT-237 SADS, NDA No. 20-344, Volume 267, page 003)
Principal Investigators: Dr. Judith Wurtman and Dr. Jerrold Bernstein

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
MIT 237	patients who were 10 to 40% above ideal body weight with Seasonal Affective Disorder Random. n=23 Completers n=18	PBO and 15 mg DF BID **TREATMENT DURATION** 4 weeks per treatment period	single center, randomized, double-blind, placebo-controlled, crossover group trial designed to examine the effects of DF administered to individuals suffering from Seasonal Affective Disorder. Each received in random order, DF 15 mg BID or PBO. These were given for 4 weeks, separated by a 2 week washout period.	1. Hamilton Depression Rating Scale* 2. Seasonal Affective Disorder Questionnaire (AAD)* a. Decreased energy b. Fatigue c. Social withdrawal d. Increased appetite e. Carbohydrate Craving f. Hypersomnia *Given at weeks 0 and 4 of each treatment period	1. Treatment with PBO was associated with a small (22%) but significant mean decline in HAM-D scores (by 4.5 ± 1.6, $p < 0.02$). Treatment with DF was associated with a highly significant reduction in HAM-D scores (by 14.8 ± 1.2, $p < 0.001$) 2. PBO treatment had no significant mean decline in AAD scores (by 1.2 ± 1.1, $p > 0.2$). DF treatment significantly reduced AAD score (by 73%, i.e., 9.7 ± 1.3; $p < 0.001$). Changes were significant in various AAD subscales, with improvements or reductions in decreased energy ($p < 0.001$), fatigue ($p < 0.001$), social withdrawal ($p < 0.001$), increased appetite ($p < 0.001$), carbohydrate craving ($p < 0.001$) and hypersomnia ($p < 0.05$). PBO diminished subjective fatigue by 25% ($p < 0.05$), compared with the 74% reduction ($p < 0.001$) seen with DF, and failed to affect any of the other subscales significantly.

"The Effect of *d*-Dexfenfluramine on Premenstrual Syndrome Associated Mood Changes and Increased Carbohydrate Consumption"
(Study Number MIT-251 PMS, **NDA No. 20-344, NDA No. 20-344, Volume 267, page 055)**
Principal Investigators: Dr. Judith Wurtman, Dr. Amnon Brzezinski and Dr. Dermott O'Rourke

STUDY	*n*	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
MIT 251	females with pre-menstrual syndrome Random. n=17 Completers n=16	PBO and DF 15 mg BID **TREATMENT DURATION** Treatment was started on the 14th cycle-day of each month and discontin-ued 2 days after the onset of menses. Thus, each subject underwent a 12 to 14 day washout period before starting subsequent treatment ; DF treatment totaled 3 sixteen day periods and PBO also totaled 3 sixteen day periods	single-center, randomized double-blind, placebo-controlled, multiple crossover study design where DF was evaluated in its ability to relieve premenstrual depression and excessive calorie intake in women with premenstrual syndrome. Subjects received DF or placebo during the luteal phases of 6 menstrual cycles, i.e., for three control and three treatment cycles each.	1. Hamilton Depression Rating Scale* 2. Activity/Mood questionnaire* on the following factors: a. appetite b. carbohydrate craving c. fatigue d. sociability e. anxiety f. work efficiency *Monthly assessments were done 2 to 3 days before expected onset of menses	1. d-F treatment significantly ($p < 0.001$) reduced the mean HAM-D Rating Scale compared with those observed during the baseline cycle or with PBO treatment. The mean HAM-D score with DF was 8 ± 1 and with PBO, 16 ± 1. 2. The Activity/Mood questionnaire scores were also significantly lower with drug treatment than with PBO ($p < 0.05$). This was due primarily to significant decreases in the appetite and carbohydrate craving subscales. No significant changes were found in the fatigue and social withdrawal subscales.

"Effects of d-Fenfluramine on Tobacco Withdrawal Symptoms, Abstinence, and Weight Gain During Smoking Cessation" (Study Number MIT-291 Smoking Cessation, **NDA No. 20-344, Volume 267, page 094**)
Principal Investigators: Dr. Richard Wurtman, Dr. Bonnie Spring and Dr. Judith Wurtman

STUDY	n	DOSE	STUDY DESIGN	BEHAVIORAL & COGNITIVE MEASURES	STUDY RESULTS
MIT 291	over-weight female smokers Random. PBO = 15 DF = 16 Completers PBO=14 DF=11	PBO or DF 15 mg BID TREATMENT DURATION 5 weeks	single-center, randomized double-blind, placebo-controlled, parallel study design where DF was evaluated in smokers to test whether caloric and carbohydrate intake increases after smoking and if DF suppresses weight gain, overeating and dysphoric mood associated with stopping smoking. Subjects began treatment phase post-baseline assessments and 1 week prior to stopping smoking and remained on treatment for 4 additional weeks post-smoking cessation.	1. Profile of Mood States* a. Tension/Anxiety Score b. Depression/Dejection Score c. Anger/Hostility Score d. Vigor/Activity Score e. Fatigue/Inertia Score f. Confusion/Bewilderment Score	1a - f. No significant difference between treatment groups in any POMS factor (baseline vs. end of treatment)
				2. Simple Auditory Reaction Time*	2. No significant difference between treatment groups
				3. Continuous Performance Test*	3. No significant difference between treatment groups in CPT, or in analysis of false positive response
				4. Letter Cancellation Test*	4. No significant difference between treatment groups in LC; DF treatment resulted in fewer false positive responses (errors), $p < 0.05$
				5. Digit Symbol Substitution Test*	5. No significant difference between treatment groups in DSST, or in analysis of false positive response
				6. Stanford Sleepiness Scale*	6. No significant difference between treatment groups
				*Analyzed at baseline and 5 weeks post-treatment (4 weeks post-stopping smoking)	

EXPERT REVIEW PANEL LETTERS AND BIOGRAPHICAL SKETCHES

APPEARS THIS WAY
ON ORIGINAL

UNIVERSITY OF LONDON
THE BETHLEM ROYAL HOSPITAL
AND
THE MAUDSLEY HOSPITAL

Clinical Psychopharmacology (MRC)
Institute Of Psychiatry

De Crespigny Park
Denmark Hill
London SE5 8AF
Tel: 0171-703 5411 Ext.3372
Fax: 0171-252 5437

Dr R E Gammans
Interneuron Pharmaceuticals Inc
99 Hayden Avenue, Suite 340
Lexington
MA 02173
USA

25 October 1995

Dear Dr Gammans

You have asked me to give my opinion on the document entitled *Evaluation of Clinical Data that pertain to the Human Risk for Adverse Neurologic, Psychiatric, Behavioral and Cognitive Effects of Dexfenfluramine*. I have examined the document in detail and note that it includes more than 10 years extensive post-marketing reporting of experiences with the drug. This, in my opinion, is a more than adequate database upon which to base an assessment of the risk of rare adverse events.

The possible effects of dexfenfluramine are addressed under several headings and in each case there are both controlled data and post-marketing data upon which to base an evaluation. I can see no evidence for any adverse effects on brain function as monitored by neurologic, psychiatric, behavioral and cognitive examinations.

In my opinion, dexfenfluramine is safe and well tolerated and the risk of any delayed adverse effects must be regarded as extremely remote.

Yours sincerely,

Malcolm Lader, D.Sc.,Ph.D., M.D.,F.R.C.Psych.
Professor of Clinical Psychopharmacology
Institute of Psychiatry
University of London
London SE5 8AF

Dr. Malcolm Lader

Dr. Lader is Professor of Clinical Psychopharmacology, Institute of Psychiatry, University of London; Member of the External Scientific Staff, Medical Research Council, and an Honorary Consultant in Psychiatry to the Bethlem Royal and Maudsley Hospital. His qualifications include: Doctor of Medicine (Psychiatry); Doctor of Philosophy (Pharmacology); Doctor of Science (Pharmacological Research); Fellow of the Royal College of Psychiatrists and Diploma in Psychological Medicine.

He was a member of the Committee on the Review of Medicines from 1978-1989. He is currently a member of the Advisory Council on the Misuse of Drugs; Trustee of the Mental Health Foundation; and a member of other national and regional advisory committees.

He was an adviser to the World Health Organization, and was vice-president of the International College of Psychopharmacology. He was also President of the Society for the Study of Addiction and President of the British Association for Psychopharmacology.

He is on the advisory boards of over 15 international scientific journals.

He has been engaged in medical research for over 30 years, with primary research interest in the drugs used in psychiatry, in particular, their side effects. His research has resulted in the publication of 12 books and about 550 scientific articles.

He conducts and supervises clinics at the Bethlem Royal and Maudsley Hospital (a Post-graduate Teaching Hospital) dealing with anxiety, sleep and depressive disorders and drug treatment problems.

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

A. John Rush, M.D.
Betty Jo Hay Distinguished Chair in Mental Health
Director, Mental Health Clinical Research Center

Department of Psychiatry
Kenneth Z. Altshuler, M.D
Chairman

October 26, 1995

Richard Gammans, Ph.D.
Vice President, Clinical Research
Interneuron Pharmaceuticals, Inc.
99 Hayden Avenue, Suite 340
Lexington, MA 02173

Dear Dr. Gammans:

I am writing to summarize my review of the issue of the long-term safety of dexfenfluramine (D-fenfluramine). I carefully read not only the reviews of the literature prepared by your staff, but quite a number of the original articles. The sum of my review is that at doses used in humans for the treatment of obesity, D-fenfluramine will have no long-term effects on CNS serotonin function (i.e., neurotoxicity).

The macaque monkey studies do show post-discontinuation CNS serotonin functional abnormalities, but there is no direct evidence of formally defined neurotoxicity. These findings in monkeys, however, are not generalizable to humans for the following reasons: (1) the doses are larger than therapeutic in some cases; (2) the metabolites generated by these animals are different than those made by humans; and (3) these animals differentially concentrate the drug and its metabolites in the CNS compared to humans.

Further evidence of long-term safety come from long-term on drug and post-discontinuation studies in humans in which psychiatric (e.g., depressive), neuropsychiatric (e.g., tests of information processing), and somatic/physiologic (e.g., appetite, weight control sleep disturbance) symptoms are not found with the drug. Most persuasive is the MRS study conducted on humans at therapeutic doses that reveals CNS concentrations of the drug that are not only quite low, but are at levels so minimal that gross 5HT concentrations are not changed.

The bottom line is that I could find no evidence of long-term neurotoxicity or neurofunctional impairment either on or off the drug in humans in therapeutic doses, nor animal studies that suggest such should be found. The long-term safety case for D-fenfluramine seems to be better established than with any new drug submitted for FDA approval.

Taken together with the medical morbidity and mortality of obesity, I would recommend this compound to any close relative, patient, or for myself, if the indication for treatment was present - given what we do know about long-term safety. I am sure the review committee will find the data quite persuasive of long-term safety as well.

Sincerely yours,

/ A. John Rush, M.D.

AJR/dls

Dr. A. John Rush

A. John Rush, M.D., holds the Betty Jo Hay Distinguished Chair in Mental Health, Department of Psychiatry, University of Texas Southwestern Medical Center in Dallas, Texas. He is a graduate of Princeton (B.A. Biochemistry, 1964); Columbia University College of Physicians and Surgeons (M.D., 1968); Northwestern University (Internship in Internal Medicine, 1969); and the University of Pennsylvania (Psychiatric Residency, 1972-75). He served in the U.S. Army (1969-71), and in the Special Action Office for Drug Abuse Prevention, Washington, D.C. (1971-72).

He is a Fellow of the American Psychiatric Association, the American College of Neuropsychopharmacology, and the American College of Psychiatry. He has served as President of the Society for Psychotherapy Research, Secretary-Treasurer of the Society of Biological Psychiatry, Chair of the DSM-IV Workgroup on Mood Disorders, and Chair of the Agency for Health Care Policy and Research Panel on Practice Guidelines for Depression. He has also served on three extramural NIMH Review Committees, the V.A. Merit Review Board, and presently chairs the NIMH Treatment Assessment Committee. He has published over 160 papers and book chapters, and six books.

For over 20 years, Dr. Rush has conducted clinical research that has spanned biological and psychosocial issues in mood disorders in adults, children and adolescents, and promoted the application of clinical research findings to improve the diagnosis and treatment for these patients. He has received the Strecker Award (Institute of Pennsylvania Hospital) and the Charles C. Burlingame Aware (Institute of Living) in recognition of his research, teaching and clinical work. He is co-recipient of the Gerald L. Klerman Lifetime Research Award from the National Depressive and Manic Depressive Association. He is also the recipient of the Dallas Alliance for the Mentally Ill 1994 Professional of the Year Award.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

THE CLINICAL RESEARCH CENTER

Paul A. Spiers, Ph.D.
Visiting Scientist
508-887-6220

77 Massachusetts Ave, E17-438
Cambridge, MA 02139
617-253-6677

October 25th, 1995

Richard E. Gammans, Ph.D.,
Vice President, Clinical Development,
Interneuron Pharmaceuticals Incorporated,
99 Hayden Avenue, Suite 340,
Lexington, MA 02173.

Dear Dr. Gammans,

I recently completed my review of your report entitled *Evaluation of Clinical Data that pertains to the Human Risk for Adverse Neurologic, Psychiatric, Behavioral and Cognitive Effects of Dexfenfluramine.* The report covers an extensive literature including placebo-controlled, clinical trials and data from a decade of post-marketing surveillance in Europe. Most importantly, there is considerable data regarding those central nervous system functions which are most likely to be adversely effected by alterations in Serotonin metabolism.

Overall, the report makes it clear that Dexfenfluramine does not appear to pose any risk of neuropsychiatric or neurocognitive adverse effects. While it remains possible that the rare individual may experience some minor adverse reaction to this compound as a function of their unique metabolism or neurochemical constitution, Dexfenfluramine appears to be well tolerated, effective in achieving its stated purpose and very safe for consumption by the general public.

In conclusion, based on my review of the data, I would not hesitate to recommend to the FDA that it approve Dexfenfluramine for use in the United States as this drug does not, within the limits of my expertise, appear to pose any risk of adverse neuropsychological effects to the central nervous system.

Sincerely,

Paul A. Spiers, Ph.D.,
Clinical Psychologist / Neuropsychologist
Neuropsychology Associates, P.C.

APPEARS THIS WAY
ON ORIGINAL

Visiting Scientist, Clinical Research Center
Massachusetts Institute of Technology.

PAS/mac

Dr. Paul A. Spiers

Dr. Spiers is a Clinical Psychologist/Neuropsychologist. He has a bachelor of arts degree (summa cum laude) from McGill University in Psychology, with honors in the area of abnormal psychology. He has a masters degree from Clark University in Clinical Psychology and a Ph.D. from the same institution in Clinical Psychology/Neuro-psychology. His formal training included training under internationally recognized experts including: Edith Kaplan, Harold Goodglass, and Norman Geschwind. He did a fellowship at the University of Paris, France, studying acalculia with Dr. Henry Hecaen. He completed his internship at the Neurobehavior Service of the V.A. Medical Center in Boston and practiced at the Harvard Medical School Behavioral Neurology Unit. Dr. Spiers has been involved with several clinical/research consultation and teaching activities at such institutions as the National Institute of Mental Health, Bethesda, M.D.; Minister of Health and Welfare, Government of Canada, Ottowa Canada; Department of Mental Health and Retardation, Commonwealth of Massachusetts. He is now a visiting professor at MIT currently studying changes in memory and cognitive function as a result of normal aging and the efficacy of new drugs which may enhance memory performance in older adults.

Dr. Spiers has published in peer-reviewed journals and authored chapters on topics ranging from drug abuse and behavioral changes associated with epilepsy, to methodology in neuropsychological testing and acalculia.

Dr. Spiers has been admitted as a qualified expert in courts, including the U.S. Supreme Court, the Federal District Court in Massachusetts and Connecticut, and other courts. He has worked as a forensic consultant for various state divisions, including, the Office of the Attorney General, in California and Kentucky; the Federal Public Defender in Pennsylvania; the Department of Justice, Criminal Division, War Crimes Bureau in Washington D.C., etc.

A Benefit/Risk Assessment of Dexfenfluramine for Treatment of Obesity

by Gerald Faich MD, MPH
President, Pharmaceutical Safety Assessments, Inc.
formerly Office Director for Statistics, Epidemiology and
Postmarketing Surveillance, FDA

Introduction

Dexfenfluramine (DF) has been used extensively for the treatment of obesity. It is serotoninergic and thus increases satiety and diminishes carbohydrate craving. Because a small number of reports in France of primary pulmonary hypertension (PPH) were reported to its manufacturer, Servier, an international case control epidemiologic study was commissioned and done between 1992 and 1995. This showed an association between all weight-loss agents and PPH. Despite the association, the absolute risk appears very small. The purpose of this paper is to examine the magnitude of the benefits and risks of the use of DF for treatment of obesity.

IPPHS

The International Primary Pulmonary Hypertension Study (IPPHS) was a case control study which sought to locate all PPH cases in 5 countries (France, Belgium, UK, Switzerland and Netherlands) over 2 years by contacting 300 tertiary care centers. A total of only 95 eligible PPH cases and 355 healthy, matched comparators were identified and interviewed about obesity and the use of anorectic agents. The study verified that PPH is an extremely rare disease occurring at an annual rate of 2 per million population. It appears that obesity itself increases risk by 2.4 fold, that short term anorectic exposure adds little risk and that the maximal excess risk for longer term (>3 months) anorectic therapy is on the order of 2 cases or 1 death per 100,000 treated for more than 3 months (odds ratio of 10.6).

Diagnostic and recall bias and confounding by obesity itself, all contributed to increasing the magnitude of the association with anorectic agents, so that the true risk may be only half this value. Moreover, since serial weights were not measured in the IPPHS, it could not assess the effects of weight loss and fluctuation which may entirely account for the anorectic association.

Obesity risk

In contrast to the rare risk of PPH, the mortality and morbidity risks of obesity are extremely common. Recent epidemiologic data from several studies quantify these risks for both men and women. For example, based on the Harvard Nurses' Health Study, an increase in Body Mass Index (BMI) from 26 to 32 (only about 15% of body weight or 15 kilograms), nearly doubles the overall risk of death and results in about 1000 excess deaths per million persons per year (see Table 1). This increase is due to increased deaths due to coronary heart disease, diabetes and cancer. It must be further recalled that for each such death there is considerable morbidity, for example, there are 4-5 myocardial infarctions for each infarction death.

Dexfenfluramine Benefit

A large (nearly 1000 patient) international, controlled trial (INDEX) has shown that obese individuals treated with both dexfenfluramine and diet will lose the following amounts of weight and maintain this loss for a year: more than 20% will lose 15% of their body weight, 20% will lose 10% of their body weight and 20% will lose 5% of their body weight.

Benefit of Weight Loss

While there is little doubt that weight gain is detrimental to health, is it reasonable to believe that weight loss will improve survival? There are a number of reasons to think this is so. First, it is clear from trial data and observations in clinical practice, that weight loss results in prompt improvements in glycemia, blood pressure and lipids. Moreover one study (Colditz) shows that the loss of only 5 kilograms reduces noninsulin diabetes by 50%! The Swedish study of severe obesity has shown "cure" rates for diabetes and hypertension of 69% and 43% respectively. Most importantly, an intentional loss of 8 kilograms has been shown (Williamson) to reduce all-cause mortality by 25% (even in those without obesity-related comorbidities).

Benefit/Risk Assessment

Suppose 100,000 obese women with a mean BMI of 32 (average -191lbs and 5'5'') are started on DF therapy. What will be their benefits and risks? To calculate the risk, IPPHS can be used. The aforementioned Harvard study can provide an estimate of benefits assuming the improvement in survival with weight loss follows the same course as the decline in survival with weight gain.

It is important to adjust for the expected discontinuation rate of 40% which reduces exposure and risk. From all this, it can be predicted that about 1 case and 1/2 PPH death (assuming a 50% case fatality rate) might occur . Over 28 obesity-related deaths will be prevented per year (see Table 2). Additionally, a number of morbid events (eg.44 surviving myocardial infarcts and strokes) will also be prevented. Thus, it is clear that the benefit to risk ratio for DF therapy is large, at least 72 when morbidity is considered.

This is a conservative estimate of the benefit-to-risk ratio since all morbidity wasn't considered (eg hip fractures), the Nurses' Health Study was based on relatively healthy individuals and the "worst case" estimate of PPH risk was used (using an odds ratio of half would double the benefit-to-risk ratio). Moreover, it is possible that benefits will continue in future years while most of the risk may be confined to the first year due to depletion of susceptibles.

It should also be noted that placebo effect with dieting could account for 50% of the benefits. However, in the "real world' of clinical practice, placebos aren't used. The placebo effect in the INDEX trial may have been due to protocol-induced effects (eg encouragement with diet compliance and frequent office visits) that also may not be operative in actual medical settings.

Summary

Primary pulmonary hypertension is a serious, but very rare event associated with the use of anorectic agents. It must be viewed in the context of the increasing prevalence of untreated obesity and its adverse consequences. Even an increase of less than 10 kilograms has very substantial survival and illness impacts. DF has been demonstrated to be effective, long term, for a substantial proportion of patients begun on it. The benefit to risk ratio for the drug is large.

Table 1-- Excess Deaths Per Million Patient Years*

BMI Changes	Increased Risk (Death)	Excess (Delta x 1076**)
27 to 32	2.2 - 1.4 = 0.80	860
28 to 32	2.2 - 1.6 = 0.60	558
29 to 32	2.2 - 1.8 = 0.40	430
30 to 32	2.2 - 2.1 = 0.10	110

* Derived from NHS-Manson-NEJM Sept .14 1995. Female, non-smokers with stable weight. Multivariate RR's adjusted for age, physical activity, diet, alcohol, hormones.
** 1076 - referent

Table 2 Deaths Avoided per 100,000 Women With a Mean BMI of 32[A] Begun on Df

No of Patients Achieving Stated Weight Loss (%)[B]	Loss kg (% Body Wt)	Resultant BMI	Deaths Avoided[C]
20,000 (20%)	13.0 (15%)	27	17.2
20,000 (20%)	8.7 (10%)	29	8.6
20,000 (20%)	4.3 (5%)	30	2.2
Lives Saved Per 100,000 Treated			28.0

[A] range 26-36, mean wt 191 lbs. and 5'5" or 87 kg and 165 cm
[B] INDEX values (conservative)
[C] no. times delta from Manson table 1 above

APPEARS THIS WAY
ON ORIGINAL

Bibliography

Benson V, Marano MA. Current estimates from the National Health Interview Survey. 1993. National Center for Health Statistics. Vital Health Stat 10(190), 1994.

Centers for Disease Control and Prevention, National Center for Health Studies. Monthly Vital Statistics Report 1994:42(No.13):1-35.

Colditz GA, Willett WC, Rotmisky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Int Med 1995; 122:481-486.

Goldstein DF. Beneficial health effects of modest weight loss. Int J Obesity 1992;16:397-415.

Lee IM, Manson JE, Hennekens CH, Paffenbarger RS. Body weight and mortality: A 27 year follow-up of middle-aged men. JAMA 1993;270:2823-2828.

Lew EA. Mortality and weight: Insured lives and the American Cancer Society studies. Ann Int Med 1985;103(6 pt 2):1024-1029.

Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality in women. New Eng J Med 333: 677-685.1995.

Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. Am J Epidemiol 1995;114:1128-1141.

INDEX Trial--regulatory submission, Interneuron Pharmaceuticals, Lexington Ma.

Sjostrum, L, Swedish Obesity Subjects Study, Abstract, 1995

Abenheim, L et al, International Primary Pulmonary Hypertension Study, First Report on the association with anorexigens, April 1995.

Redacted 3

pages of trade

secret and/or

confidential

commercial

information