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N-18677-1

NDA 18-677

AP / LTR

NDA 18-677

DEC 26 1985

Eli Lilly and Company
Attention: Max W. Talbott, Ph.D.
307 East McCarty Street
Indianapolis, Indiana 46285

Dear Dr. Talbott:

Reference is made to your new drug application dated February 16, 1982, submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for the preparation CESAMET (nabilone).

We additionally acknowledge receipt of your amendments dated December 13 and 18, 1985.

We have completed the review of this application including the submitted draft labeling and the application is approved, effective on the date of this letter. However, the labeling must be revised exactly as we have requested in the addendum to this letter. In particular, please note that we could not employ the tabulations of ADRs presented in your draft labeling proposal as they were derived from a combination of controlled and open clinical experience. We have, therefore, substituted two tables derived from our review of the controlled investigations in your application. In addition, we have made some minor revisions of your proposed labeling text to produce consistency in the labeling of cannabinoid drug products.

Twelve copies of the final printed version of the revised labeling (including container and package labeling) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

We note your agreement to accept an interim dissolution specification [Q equal to 70% in 60 minutes (USP method II, 50 rpm, 1000 ml of 0.1% aqueous Tween 80, 37 degrees C) for the rotary evaporation process capsule intended for marketing], as discussed in a December 17, 1985 telephone conversation between Drs. Childers and Hirsch of your firm and Dr. Paul Hepp of the agency's Division of Biopharmaceutics.

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

Please submit one market package of the drug when available.

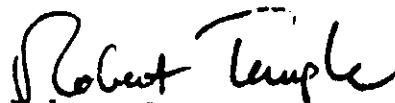
NDA 18-677

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We wish to remind you that CESAMET may not be legally marketed until the Drug Enforcement Administration has completed scheduling activities as required by the Controlled Substances Act.

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

Sincerely yours,



Robert Temple, M.D.

Director

Office of Drug Research and Review
Center for Drugs and Biologics

ATTACHMENT

ADDENDUM TO APPROVAL LETTER (NDA 18-677)

[NOTE TO FIRM: Please include the Controlled Substances Symbol C-II in your labeling as appropriate]

CESAMET
NABILONE
PULVULES (Capsules)

DESCRIPTION:

CESAMET brand of nabilone is a synthetic cannabinoid for oral administration. Nabilone as a raw material occurs as a white polymorphic crystalline powder. In aqueous media, the solubility of nabilone is less than 0.5 mcg per ml, with pH values ranging from 1.2 to 7.0.

Chemically, nabilone is (+)-trans-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one and has the empirical formula $C_{24}H_{36}O_3$. It has a molecular weight of 372.55. The structural formula is as follows:

[NOTE TO FIRM: PLACE STRUCTURAL FORMULA HERE WHICH CONFORMS TO THAT INCLUDED IN THE USAN DICTIONARY (1985) FOR NABILONE, page 335.]

Each CESAMET Pulvule (Capsule) contains 1 mg nabilone.

CLINICAL PHARMACOLOGY:

Non-Therapeutic Effects

CESAMET, a synthetic cannabinoid, is highly abusable and has the potential to produce psychological dependence. CESAMET has complex effects upon the central nervous system. Its effects upon the mental state (i.e., "inner mental life") are similar to cannabis. Subjects administered CESAMET experience changes in mood (euphoria, detachment, depression, anxiety, panic, paranoia, etc.), decrements in cognitive performance and memory, a decreased ability to control drives and impulses, and alterations in the experience of reality (e.g., distortions in the perception of objects and the sense of time, hallucinations, etc.). These phenomena appear to be more common when larger doses of CESAMET are administered; however, a full blown picture of psychosis (psychotic organic brain syndrome) may occur in patients receiving doses within the lower portion of the therapeutic range.

Data on the chronic use of CESAMET are not available; experience with cannabis suggests that chronic use of cannabinoids may be associated with a variety of untoward effects on motivation, cognition, judgment, etc., but whether these phenomena reflect the underlying character of individuals chronically abusing cannabis or are a result of the use of cannabis is not known.

The simultaneous use of CESAMET and alcohol or barbiturates may produce additive depressive effects upon central nervous system function. Possible changes in mood and other adverse behavioral effects may occur in patients receiving CESAMET. Patients should remain under supervision of a responsible adult while using CESAMET.

CESAMET has central nervous system activity. It produces relaxation, drowsiness, and euphoria in the recommended dose range. Tolerance to these effects develops rapidly and is readily reversible.

Beyond effects on the mental state, CESAMET has several systemic actions; most prominent are dry mouth and hypotension. CESAMET has been observed to elevate supine and standing heart rates and to cause supine and orthostatic hypotension. In clinical studies, oral administration of 2 mg of CESAMET did produce some decrease in airway resistance in normal controls, but had no effect in patients with asthma. No other non-therapeutic effects of CESAMET of clinical significance have been reported.

Metabolism and Pharmacokinetics

Following oral administration of CESAMET Pulvules, peak plasma concentrations of nabilone occur within about 2 hours. Precise information concerning the relative accumulation of nabilone and its 'active' metabolites after repeated administration is not available. Available evidence suggests, however, that one or more of the metabolites have terminal elimination half-lives that exceed that of nabilone. Consequently, in repeated use, the metabolites may accumulate to concentrations in excess of the parent.

The extent to which nabilone undergoes presystemic clearance (first pass effect) is unknown. Metabolism of nabilone, however, is extensive and several metabolites have been identified. The relative activity of the metabolites and the parent drug has not been established. Following oral administration of a 2 mg dose of radiolabeled nabilone, peak serum nabilone concentrations of approximately 10 ng/ml are achieved. The plasma half life ($T_{1/2}$) values for nabilone and total radioactivity (identified and unidentified metabolites) are about 2 and 35 hours, respectively. Dose proportionality for the parent drug and its metabolites have not been determined. The effects of age, hepatic dysfunction, and renal insufficiency on the metabolism and elimination of nabilone have not been determined.

When CESAMET is administered orally or intravenously, the drug and its metabolites are eliminated in feces (approximately 65%) and to a lesser extent in urine (approximately 20%). It appears that the major excretory pathway is the biliary system.

INDICATIONS AND USAGE:

CESAMET Pulvules (Capsules) are indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. This restriction is required because a substantial proportion of any group of patients treated with CESAMET can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents.

Because of its potential to alter the mental state, CESAMET is intended for use under circumstances which permit close supervision of the patient by a responsible individual.

CESAMET is highly abusable and controlled as nabilone under Schedule II of the Controlled Substances Act. Prescriptions for CESAMET should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).

Evidence supporting the efficacy of CESAMET in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from both active-controlled (prochlorperazine) and placebo-controlled trials. Persuasive evidence was obtained in subjects being treated with a wide variety of chemotherapy regimens, including low dose cisplatin (20mg/M²).

CONTRAINDICATIONS:

CESAMET is contraindicated in patients whose nausea and vomiting arises from any cause other than cancer chemotherapy.

CESAMET is contraindicated in any patient known to be hypersensitive to it.

WARNINGS:

Because of its profound effects on the mental status, patients should be warned not to drive, operate complex machinery, or engage in any activity requiring sound judgment and unimpaired coordination while receiving treatment with CESAMET. The effects of CESAMET may persist for a variable and unpredictable period of time following its oral administration. Adverse psychiatric reactions can persist for 48 to 72 hours following treatment cessation. Because of individual variation in response and tolerance to the effects of CESAMET, the physician should determine on clinical grounds the period of patient supervision required. Patients receiving CESAMET should be closely observed, if possible, within an inpatient setting. This is especially important during the treatment of naive patients. However, even patients experienced with CESAMET or cannabis may have serious untoward responses not predicted by prior uneventful exposures. Because a psychotic patient is a potential danger to him/herself and/or others, any patient who has a psychotic experience with CESAMET should be closely observed in an appropriate setting until his/her mental state returns to normal. The patient should not be given additional doses of CESAMET until he/she has been examined, and the circumstances evaluated, by a physician. If the clinical situation warrants it, a lower dose of CESAMET may be administered under very close supervision. The patient should be counseled about the experience and should share in the decision about further use of CESAMET.

CESAMET should not be taken with alcohol, sedatives, hypnotics or other psychotomimetic substances.

PRECAUTIONS:General

Since CESAMET brand of nabilone elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in the elderly, and in patients with hypertension or heart disease.

CESAMET should also be used with caution in patients with current or previous psychiatric disorders, (including manic depressive illness and schizophrenia) as the symptoms of these disease states may be unmasked by the use of cannabinoids.

CESAMET should be used with caution in individuals receiving other psychoactive drugs.

Information for patients

Persons taking CESAMET should be alerted to the additive central nervous system depression resulting from simultaneous use of CESAMET and alcohol or barbiturates. This combination should be avoided. Operation of machinery or a motor vehicle should be avoided during CESAMET therapy. Patients using CESAMET should be made aware of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under supervision of a responsible adult while using CESAMET.

Drug Interactions

Potential interactions between CESAMET 2 mg, and diazepam 5 mg; sodium secobarbital 100 mg; alcohol 45 ml (absolute laboratory alcohol); or codeine 65 mg, were evaluated in 15 subjects. Only a single combination was utilized at any one time. The subjects were evaluated according to physiologic (i.e., heart rate and blood pressure), psychometric, psychomotor, and subjective parameters. In this study, as expected, the depressant effects of the combinations were additive. Psychomotor function was particularly impaired with diazepam combination. Caution must thus be used when administering nabilone in combination with any CNS depressant.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been performed with CESAMET. The influence of CESAMET on fertility and reproduction was evaluated in rats and rabbits at doses of 150 and 40 times the maximum recommended human dose, respectively. In these studies there was no evidence of teratogenicity due to CESAMET. In high dose groups, however, CESAMET produced a decrease in pregnancy rate.

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats at 150 times the human dose and rabbits at 40 times the human dose revealed a dose related reduction in litter size, an increase in the incidence of fetal resorptions and an increase in the incidence of stillborn pups. These affects appear related to the dose dependent reduction in maternal food intake and body weight gain induced by CESAMET. At 150 times the maximum recommended human dose, CESAMET produced a reduction in neonatal survival that may be related to reduced milk production by mothers. CESAMET is known to have an inhibitory effect on prolactin release which could contribute to the observed reduction in milk production. Hypothermia was also reported in the offspring of high dose female rats, which may have also contributed to reduced neonatal survival. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in breast milk. Because many drugs are excreted in breast milk, it is not recommended that CESAMET be given to nursing mothers.

Pediatric Use

Safety and effectiveness have not been established in patients younger than 18 years of age.

ADVERSE REACTIONS:

Commonly Encountered Reactions

During controlled clinical trials of CESAMET, virtually all patients experienced at least one adverse reaction. The most commonly encountered events were drowsiness, vertigo, dry mouth, euphoria (high), and headache.

Comparative Incidence of Reactions

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the tables presented below are presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of CESAMET under relatively similar conditions of use. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of CESAMET is provided in the WARNINGS and PRECAUTIONS sections.

The following tables list in order of decreasing frequency for CESAMET the adverse reactions encountered by a substantial proportion of the CESAMET-treated patients participating in representative controlled clinical trials.

Table
INCIDENCE OF ADVERSE REACTIONS COMPARED TO PLACEBO

<u>ADR</u>	Nabilone (n = 134)		Placebo (n = 119)	
	<u>Patients</u>	<u>Percent</u>	<u>Patients</u>	<u>Percent</u>
Vertigo	69	51	3	2.5
Drowsiness	69	51	6	5
Dry Mouth	47	35	2	1.7
Ataxia	19	14	0	0
Euphoria	14	10.4	1	0.8
Sleep Disturbance	14	10.4	1	0.8
Dysphoria	12	9	0	0
Headache	8	6	0	0
Nausea	5	3.7	0	0
Disorientation	3	2.2	0	0
Depersonalization	2	1.5	1	0.8

Table
INCIDENCE OF ADVERSE REACTIONS IN
ACTIVE CONTROLLED STUDIES

<u>ADR</u>	Nabilone (n = 250)		Prochlorperazine (n = 232)	
	<u>Patients</u>	<u>Percent</u>	<u>Patients</u>	<u>Percent</u>
Drowsiness	165	66	108	47
Vertigo	111	44	42	18
Dry Mouth	102	41	10	4
High	95	38	12	5
Concentration Difficulties	62	25	3	1
Dizziness	36	14	11	5
Depression	35	14	37	16
Ataxia	31	12	4	2
Headache	30	12	12	5
Visual Disturbance	30	12	9	4
Asthenia	20	8	4	2
Anorexia	19	8	22	9
Hypotension	17	7	2	1
Sedation	14	6	2	1
Increased Appetite	12	5	0	0

Adverse Reactions by Body System

The following listing of adverse events is organized by decreasing frequency within body systems for CESAMET-treated patients in controlled clinical trials. All events are listed regardless of causality assessment.

- I. BLOOD AND HEMATOPOETIC: Anemia
- II. CARDIOVASCULAR: Orthostatic Hypotension; Hypotension; Tachycardia; Syncope; Palpitation; Flushing; Hypertension; Arrhythmia; and Cerebral Vascular Accident.
- III. EYE AND EAR: Vision Disturbance; Ear Tightness; Eye Irritation; Eye Dryness; Equilibrium Dysfunction; Tinnitus; Eye Disorder; Amblyopia; Eye Swelling; Eyelid Diseases; Pupil Dilation; Photophobia; and Visual Field Defect.
- IV. GASTROINTESTINAL: Dry Mouth; Nausea; Anorexia; Vomiting; Diarrhea; Abdominal Pain; Constipation; Aphthous Ulcer; Mouth Irritation; Gastritis; and Dyspepsia.
- V. GENITO-URINARY: Increased Urination; Decreased Urination; Hot Flashes; Urinary Retention; and Frequency of Micturition.
- VI. INFECTION: Bacterial Infection
- VII. METABOLIC AND ENDOCRINE: Thirst
- VIII. MUSCULOSKELETAL: Muscle Pain; Back Pain; Neck Pain; Joint Pain; and Unspecified Pain.
- IX. NERVOUS SYSTEM: Drowsiness; Vertigo; Ataxia; Concentration Decreased; Sedation; Hallucinations; Paresthesiae; Tremor; Memory Disturbance; Perception Disturbance; Convulsions; Dystonia; Numbness; and Akathisia
- X. PSYCHIATRIC: Euphoria (High); Sleep Disturbance; Depression; Confusion; Disorientation; Anxiety; Depersonalization Syndrome; Speech Disorder; Abnormal Dreams; Insomnia; Mood Swings; Inebriated Feeling; Toxic Psychosis; Paranoia; Apathy; Thought Disorder; Withdrawal; Panic Disorder; Phobic Neurosis; Emotional Disorder; and Hyperactivity.
- XI. RESPIRATORY: Dyspnea; Pharyngitis; Nasal Congestion; Sinus Headache; Thick Tongue; Dry Throat; Dry Nose; Wheezing; Nosebleed; Cough; Voice Change; and Chest Pain.
- XII. SKIN AND APPENDAGES: Anhidrosis; Photosensitivity; Pruritus; Rash; and Allergic Reactions.

- XIII. MISCELLANEOUS AND ILL-DEFINED CONDITIONS: Headache; Fatigue; Lightheadedness; Coordination Disturbance; Asthesia; Dyphoria; Dizziness; Taste Change; Excessive Appetite; Chills; Excessive Sweating; Nervousness; Malaise; Postural Dizziness; Twitch; Irritability; Fever; Inhibited Walking; Unconscious; Hypotonia; and Impaired Urination.

Spontaneously Reported Adverse Reactions

CESAMET has been marketed internationally since 1982. The following list of body systems describes, in order of decreasing frequency, the adverse events reported from the marketed use of CESAMET. All events are listed regardless of causality assessment.

- I. BLOOD AND HEMATOPOETIC: Leukopenia
- II. CARDIOVASCULAR: Hypotension; and Tachycardia
- III. EYE AND EAR: Visual Disturbances
- IV. GASTROINTESTINAL: Dry Mouth; Nausea; Vomiting; and Constipation
- V. NERVOUS SYSTEM: Hallucinations; CNS Depression; CNS Stimulation; Ataxia; Stupor; Vertigo; Convulsion; and Circumoral paresthesia
- VI. PSYCHIATRIC: Somnolence; Confusion; Euphoria; Depression; Dysphoria; Depersonalization; Anxiety; Psychosis; and Emotional Lability
- VII. MISCELLANEOUS AND ILL-DEFINED CONDITIONS: Dizziness; Headache; Insomnia; Abnormal Thinking; Chest Pain; Lack of Effect; and Face Edema

DRUG ABUSE AND DEPENDENCE:

CESAMET, a synthetic cannabinoid that is closely related to dronabinol (formerly known as delta-9-THC), is a highly abusable substance. CESAMET is controlled under Schedule II of the Controlled Substances Act. Prescriptions for CESAMET should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).

It is not known what proportion of individuals exposed chronically to CESAMET or other cannabinoids will develop either psychological or physical dependence. Long term use of these compounds has, however, been associated with disorders of motivation, judgment, and cognition. It is not clear, though, if this is a manifestation of the underlying personalities of chronic users of this class of drugs or if cannabinoids are directly responsible for these effects. An abstinence syndrome has been reported following discontinuation of high doses of dronabinol (200 mg per day). The acute phase was characterized by psychic distress, insomnia, and signs of autonomic hyperactivity (sweating, rhinorrhea, loose stools, hiccoughs). A protracted abstinence phase may have occurred as subjects reported sleep disturbances for several weeks after delta-9-THC discontinuation.

CESAMET may produce subjective side effects which may be interpreted as a euphoria or marijuana-like "high" at therapeutic doses. CESAMET was shown to be qualitatively and quantitatively similar to delta-9-THC in the production of cannabis-like effects, thus demonstrating CESAMET has a high potential for abuse.

Preclinical studies performed in both dogs and monkeys demonstrated that CESAMET was cannabinoid-like. As with delta-9-THC, tolerance develops rapidly to the pharmacological effects in both the dog and the monkey. Cross tolerance between CESAMET and delta-9-THC was demonstrated in the monkey.

The physical dependence capacity of CESAMET is unknown at this time. Patients who participated in clinical trials of up to 5 days' duration evidenced no withdrawal symptomatology upon cessation of dosing.

OVERDOSAGE:

Signs and symptoms of overdose are an extension of the psychotomimetic and physiologic effects of CESAMET, and therefore, the clinical picture of overdose may vary widely from patient to patient. Overdosages may be considered to be of two types: those at therapeutic doses and those at higher, supra-therapeutic, doses.

Overdosage at Prescribed Dosages

Overdosage may be considered to have occurred even at prescribed dosages if disturbing psychiatric symptoms have occurred. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be held until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated; in such instances, a lower initiating dose is suggested. In controlled clinical trials, alterations in mental status related to the use of CESAMET resolved within 72 hours without specific medical therapy.

In overdose settings, attention should be paid to the vital signs, as both hypertension and hypotension are known to occur.

Overdosage at Multiples of Prescribed Dosages

No cases of overdose with nabilone of greater than 10 mg/day were reported during clinical trials. In addition, no reports of overdose have been observed in the marketing of CESAMET elsewhere in the world. Signs and symptoms that would be expected to occur in large overdose situations are psychotic episodes including hallucinations, anxiety reactions, respiratory depression, and coma.

If psychotic episodes occur, the patient should be managed conservatively, if possible. For moderate psychotic episodes and anxiety reactions, verbal support and comforting may be sufficient. In more severe cases, antipsychotic drugs may be useful; however, the utility of antipsychotic drugs in

cannabinoid psychosis has not been systematically evaluated. Support for their use is drawn from limited experience using antipsychotic agents to manage cannabis overdoses. Because of the potential for drug-drug interactions (e.g., nabilone and chlorpromazine are CNS depressants with additive effects) such patients should be closely monitored.

Treatment for respiratory depression and comatose state consists of symptomatic and supportive therapy. Particular attention should be paid to the occurrence of hypothermia.

DOSAGE AND ADMINISTRATION:

The usual adult dosage is 1 or 2 mg b. i. d. On the day of chemotherapy, the initial dose should be given 1 to 3 hours before the oncolytic agent is administered. To minimize side effects, it is recommended that the lower starting dose be used and that dose be increased as necessary. A dose of 1 or 2 mg the night before may be useful. The maximum recommended daily dose is 6 mg given in divided doses t. i. d.

CESAMET may be administered 2 or 3 times daily during the entire course of each cycle of chemotherapy and, if needed, for 48 hours after the last dose of each cycle of chemotherapy.

HOW SUPPLIED:

Pulvules (Capsules):

1 mg (blue and white) No. 3101;
NDC 002-3101-25--25; NDC 002-3101-50--50

ANIMAL PHARMACOLOGY and/or ANIMAL TOXICOLOGY:

Monkeys treated with CESAMET at doses as high as 2 mg/kg/day for a year experienced no adverse events of significance. This result contrasts with the findings in a planned one year dog study that was prematurely terminated because of deaths associated with convulsions in dogs receiving as little as 0.5 mg/kg/day. The earliest deaths, however, occurred at 104 days in dogs receiving 1 mg/kg/day. The unusual vulnerability of the dog to CESAMET is not understood; it is hypothesized, however, that the explanation lies in the fact that the dog differs from other species in its metabolism of CESAMET.

AE LTR

NOV - 8 1985

NDA 18-677

Eli Lilly and Company
Attention: Max W. Talbott, Ph.D.
307 East McCarty Street
Indianapolis, Indiana 46285

Dear Dr. Talbott:

Please refer to your new drug application dated February 16, 1982, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the preparation CESAMET (nabilone).

We also acknowledge receipt of your additional communications dated: April 23 and 24; May 19; June 28; July 22; August 17; and September 22, 1982; February 22, 1982(sic.); March 14, 15 and 28(2 letters); May 19; September 16; and December 9, 1983; April 16, 26, and 30; May 8; August 1 and 9; and November 19, 1984; and January 28; February 13; March 28; April 29; July 8 and 26; September 20; and October 15, 1985.

We have completed the review of this amended application as submitted with draft labeling, and find it approvable.

We additionally note that your original submission provided for both a 1 mg and 2 mg capsule strength. However, your October 15, 1985 amendment states that you intend to market only the 1 mg capsule. Therefore, this letter refers to the marketing of a 1 mg capsule (granulation formulation). Alternatively, it may be possible to approve another dosage form (See next section).

Four major requirements must be met before approval of this application can be granted:

- A. Please submit a limited safety update covering the interval since your amendment dated September 20, 1985, including all deaths and any adverse events that led to discontinuation of the drug. The update should cover all studies and uses of the drug, including those involving indications not being sought in the present submission, other dosage forms or dose levels, etc.

Additionally, your report should specifically address your experience, both domestic and international, with regard to drug abuse and/or diversion of CESAMET.

- B. We are concerned that the 1 mg capsule formulation proposed for marketing (produced by the 'granulation' process), may not be bioequivalent to the 2 mg capsule formulation (produced by the 'rotary evaporation' process) used in the studies which we have relied upon as the basis for our decision that CESAMET is an effective antiemetic. Our specific concern is the possibility that the 1 mg granulation formulation may be more rapidly

absorbed than the formulation used in Phase III studies. As rapidity of absorption is known to influence CNS side effects, we wish to gain some assurance that the marketed product will NOT be more difficult and risky to use than the product employed in clinical studies.

Therefore, as a requirement for approval of the 1 mg formulation, we request that a single-dose, crossover, bioequivalence study be performed, evaluated, and submitted to the agency prior to approval. However, if you can provide evidence that our concern about increased rate of systemic bioavailability of the granulation process formulation is unfounded, we would consider deferring this study to Phase IV. Alternatively, we are prepared to approve the 2 mg rotary evaporated product. In either case, our staff is able to meet to discuss this matter.

- C. We ask you to agree to conduct and complete in a timely fashion appropriate studies designed to evaluate CESAMET's absorption, distribution, metabolism, and excretion. The design of these studies should be negotiated with our Division of Biopharmaceutics, and the studies should be performed and the results submitted within the first year of marketing. The studies required include:
1. A dose proportionality study performed over the clinical dosing range in which CESAMET will be administered. Your study should have the capacity to detect C_{min} concentrations of both the product and its principle active metabolites during multiple dosing in patients to assess the potential for accumulation under the conditions of probable clinical use.
 2. We request that you submit the results of protocols 41, 42, and 43.

We also note that additional in vivo studies may be required for fulfillment of the Biopharmaceutic requirements, dependent upon our review of the results of the studies.

Please forward three samples of 100 units each of the 1 mg CESAMET Capsules from lot CT 5055-0A, as well as from a lot intended for marketing, with manufacture and expiration dates to:

Dr. V.K. Prasad
FOB-8, Room 6076, HHS-224
200 "C" Street, S.W.
Washington, D.C. 20204

With regard to your proposed dissolution specification, we request that you upgrade your dissolution specification to at least a Q-value of 80% in 60 minutes; rather than your proposed specification of Q-75% in 60 minutes.

- D. You must extensively revise the submitted draft labeling. The revised draft labeling, however, should be presented in final format. (We recommend that the number of copies of draft labeling be limited because additional revisions may be required.)

The labeling should follow the outline provided below. In instances where we propose specific wording, please use the text verbatim unless you wish to propose and support a specific alternative. In instances where we ask that you draft new text, please provide an annotated draft supporting the statements made. (The annotations will not be included in the final labeling, but are essential for our review and evaluation.) Specific instructions are embedded in brackets [] within the text of the labeling outline.

Your labeling should include the symbol "C-II" as required by the Controlled Substances Act, in anticipation of the proposed rescheduling of CESAMET from C-I to C-II. We remind you that marketing cannot occur until the Drug Enforcement Administration completes this action.

Draft Labeling:

CESAMET
NABILONE
PULVULES (Capsules)

DESCRIPTION:

CESAMET brand of nabilone is a synthetic cannabinoid for oral administration. Nabilone occurs as a white polymorphic crystalline powder. In aqueous media, the solubility of nabilone is less than 0.5 mcg per ml, with pH values ranging from 1.2 to 7.0.

Chemically, nabilone is (+)trans-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one and has the empirical formula $C_{24}H_{36}O_3$. It has a molecular weight of 372.29. The structural formula is as follows:

[NOTE TO FIRM: PLACE STRUCTURAL FORMULA HERE WHICH CONFORMS TO THAT INCLUDED IN THE USAN DICTIONARY (1985) FOR NABILONE, page 335.]

Each CESAMET Pulvule (Capsule) contains 1 mg nabilone.

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CESAMET, a synthetic cannabinoid, is highly abusable and can produce both physical and psychological dependence. CESAMET has complex effects upon the central nervous system. Its effects upon the mental state (i.e., "inner mental life") are similar to cannabis. Subjects administered CESAMET experience changes in mood (euphoria, detachment, depression, anxiety, panic, paranoia, etc.), decrements in cognitive performance and memory, a decrease of

to control drives and impulses, and alterations in the experience of reality (e.g., distortions in the perception of objects and the sense of time, hallucinations, etc.). These phenomena appear to be more common when larger doses of CESAMET are administered; however, a full blown picture of psychosis (psychotic organic brain syndrome) may occur in patients receiving doses within the lower portion of the therapeutic range.

Data on the chronic use of CESAMET are not available; experience with cannabis suggests that chronic use of cannabinoids may be associated with a variety of untoward effects on motivation, cognition, judgment, etc., but whether these phenomena reflect the underlying character of individuals chronically abusing cannabis or are a result of the use of cannabis is not known.

Beyond effects on the mental state, CESAMET has several systemic actions; most prominent are dry mouth, hypotension (supine and orthostatic), and drowsiness.

[NOTE TO FIRM: Please draft a section that systematically reviews the known effects of CESAMET on the function of the major human organ systems. Your draft should be annotated and accompanied by reprints of the studies cited. The final labeling, however, will appear in an unannotated version. In particular, effects on the nervous system other than those mentioned earlier (e.g., whether CESAMET alters the seizure threshold, affects neurotransmission, alters thermoregulation, etc.), and effects on the autonomic nervous system, heart, vascular system, respiration, liver and gastrointestinal function, renal and genitourinary function, endocrine function, and reproduction should be summarized.]

Metabolism and Pharmacokinetics

[NOTE TO FIRM: Please draft a section that systematically reviews available absorption, distribution, metabolism, and excretion information for nabilone. This section will need to be revised when results of your phase IV bioavailability studies have been performed, evaluated and accepted by our Division of Biopharmaceutics].

INDICATIONS AND USAGE:

CESAMET Pulvules (Capsules) are indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. This restriction is required because a substantial proportion of any group of patients treated with CESAMET can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents.

Because of its potential to alter the mental state, CESAMET is intended for use under circumstances which permit close supervision of the patient by a responsible individual.

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CESAMET is highly abusable and controlled under Schedule II of the Controlled Substances Act. Prescriptions of CESAMET should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).

Evidence supporting the efficacy of CESAMET in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from both active-controlled (prochlorperazine) and placebo-controlled trials. Persuasive evidence was obtained in subjects being treated with a wide variety of chemotherapy regimens, including low dose cisplatin (20 mg/M²).

CONTRAINDICATIONS:

CESAMET is contraindicated in patients whose nausea and vomiting arises from any cause other than cancer chemotherapy.

CESAMET is contraindicated in any patient known to be hypersensitive to it.

WARNINGS:

Because of its profound effects on the mental status, patients should be warned not to drive, operate complex machinery, or engage in any activity requiring sound judgment and unimpaired coordination while receiving treatment with CESAMET. The effects of CESAMET may persist for a variable and unpredictable period of time following its oral administration. Adverse psychiatric reactions can persist for 48 to 72 hours following treatment cessation. Because of individual variation in response and tolerance to the effects of CESAMET, the physician should determine on clinical grounds the period of patient supervision required. Patients receiving CESAMET should be closely observed, if possible, within an inpatient setting. This is especially important during the treatment of naive patients. However, even patients experienced with CESAMET or cannabis may have serious untoward responses not predicted by prior uneventful exposures. Because a psychotic patient is a potential danger to him/herself and/or others, any patient who has a psychotic experience with CESAMET should be closely observed in an appropriate setting until his/her mental state returns to normal. The patient should not be given additional doses of CESAMET until he/she has been examined, and the circumstances evaluated, by a physician. If the clinical situation warrants it, a lower dose of CESAMET may be administered under very close supervision. The patient should be counseled about the experience and should share in the decision about further use of CESAMET.

CESAMET should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances.

PRECAUTIONS:

Since CESAMET brand of nabilone elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in patients with hypertension or heart disease.

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CESAMET should also be used with caution in patients with current or previous psychiatric disorders (including manic depressive illness and schizophrenia) as the symptoms of these disease states may be unmasked by the use of cannabinoids.

CESAMET should be used with caution in individuals receiving other psychoactive drugs.

Information for patients

Persons taking CESAMET should be alerted to the additive central nervous system depression resulting from simultaneous use of CESAMET and alcohol or barbiturates. This combination should be avoided. Operation of machinery or a motor vehicle should be avoided during CESAMET therapy. Patients using CESAMET should be made aware of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under supervision of a responsible adult while using CESAMET.

Drug Interactions

[NOTE TO THE FIRM: please draft an appropriate text for this section as outlined in 21 CFR 201.57(f).]

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been performed with CESAMET. The influence of CESAMET on fertility and reproduction was evaluated in rats and rabbits at doses of 150 and 40 times the maximum recommended human dose, respectively. In high dose groups, CESAMET produces a decrease in pregnancy rate. In these studies there was no evidence of teratogenicity due to CESAMET.

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats at 150 times the human dose and rabbits at 40 times the human dose revealed a dose related reduction in litter size, an increase in the incidence of fetal resorptions and an increase in the incidence of stillborn pups. These effects appear related to the dose dependent reduction in maternal food intake and body weight gain induced by CESAMET. At 150 times the maximum recommended human dose, CESAMET produced a reduction in neonatal survival that may be related to reduced milk production by mothers. CESAMET is known to have an inhibitory effect on prolactin release which could contribute to the observed reduction in milk production. Hypothermia was also reported in the offspring of high dose female rats, which may have also contributed to reduced neonatal survival. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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Nursing Mothers

[NOTE TO FIRM: Please draft a section discussing the available information regarding the appearance of nabilone in human milk.]

Pediatric Use

Safety and effectiveness have not been established in patients younger than 18 years of age.

ADVERSE REACTIONS:

[NOTE TO FIRM: This section should consist of the following:

- A. An introductory statement in narrative style that enumerates the more common reactions encountered with the use of CESAMET listing the effects which represent pharmacological extensions of drug action, (i.e., what the physician and the patient may expect in routine use);
- B. A table showing the comparative incidence of adverse effects encountered during the controlled trials;
- C. A list of all adverse reactions, organized by body system or symptom class in the manner traditionally found in this section of the package insert; and finally,
- D. A list of all adverse reactions encountered in non-domestic, post-marketing experience.

The data from all centers employing placebo and CESAMET in Protocol 28 (except center # 005, Dr Levitt) may be pooled in order to calculate and compare incidence rates for each treatment, as may data from studies employing CESAMET and active controls. (Note: All patients from active and placebo-controlled trials should be entered, including patients in Protocol 28 not submitted to the NDA at the time of filing). The incidence rates derived from the active control and placebo control studies should be listed in separate tables.]

DRUG ABUSE AND DEPENDENCE:

CESAMET is highly abusable and controlled as nabilone under Schedule II of the Controlled Substances Act. Prescriptions for CESAMET should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).

It is not known what proportion of individuals exposed chronically to CESAMET or other cannabinoids will develop either psychological or physical dependence. Long term use of these compounds has, however, been associated with disorders of motivation, judgment, and cognition. It is not clear, though, if this is a manifestation of the underlying personalities of chronic users of this class of drugs, or if cannabinoids are directly responsible.

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these effects. An abstinence syndrome has been reported following discontinuation of high doses of dronabinol (210 mg per day). The acute phase was characterized by psychic distress, insomnia, and signs of autonomic hyperactivity (sweating, rhinorrhea, loose stools, hiccoughs). A protracted abstinence phase may have occurred as subjects reported sleep disturbances for several weeks after delta-9-THC discontinuation.

CESAMET may produce subjective side effects which may be interpreted as a euphoria or marijuana-like "high" at therapeutic doses. CESAMET was shown to be qualitatively and quantitatively similar to delta-9-THC in the production of cannabis-like effects, thus demonstrating CESAMET has a high potential for abuse.

Preclinical studies performed in both dogs and monkeys demonstrated that CESAMET was cannabinoid-like. As with delta-9-THC, tolerance develops rapidly to the pharmacological effects in both the dog and the monkey. Cross tolerance between CESAMET and delta-9-THC was demonstrated in the monkey.

The physical dependence capacity of CESAMET is unknown at this time. Patients who participated in clinical trials of up to 5 days' duration evidenced no withdrawal symptomatology upon cessation of dosing.

OVERDOSAGE:

Signs and symptoms of overdosage are an extension of the psychotomimetic and physiologic effects of CESAMET, and therefore the clinical picture of overdosage may vary widely from patient to patient. Overdosages may be considered to be of two types: those at therapeutic doses, and those at higher, supra-therapeutic, doses.

Overdosage at Prescribed Dosages

Overdosage may be considered to have occurred even at prescribed dosages if disturbing psychiatric symptoms have occurred. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be held until patients have returned to baseline; routine dosing may then be resumed if clinically indicated, though this should be at a lower dosage. In controlled clinical trials, all such disturbing reactions spontaneously disappeared within 72 hours without specific medical therapy.

Particular attention should be paid to the vital signs in these patients, as both hyper- and hypotension are known to occur. These signs should be monitored and treated if necessary in the usual manner according to the judgement of the physician.

Overdosage at Multiples of Prescribed Dosages

[NOTE TO FIRMS: This sub-section should contain all known information obtained from high dose Phase I and II data (including signs following parenteral administration) as well as any information obtained from cases of accidental or intentional overdosage in countries where CESAMET has been marketed.]

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DOSAGE AND ADMINISTRATION:

The usual daily dosage of 2 mg b.i.d. is also the recommended maximum daily dose. The first dose should be administered the night before initiating administration of chemotherapeutic agents, and the second dose should be given 1 to 3 hours before the first dose of oncolytic agent is administered.

CESAMET may be administered twice daily during the entire course of each cycle of chemotherapy and, if needed, for 48 hours after the last dose of each cycle of chemotherapy.

[NOTE TO FIRM: If you believe that physicians will tend to select and/or modify the recommended dose of CESAMET, please draft a paragraph which provides suggestions for titration of the dose (e.g., for those patients experiencing side effects at the recommended dosages, and for whom lower doses would be appropriate).]

HOW SUPPLIED:

Pulvules (Capsules):

1 mg (blue and white) No. 3103), NDC 002-3101-66--1000;
NDC 002-3101-66--1010; NDC 002-3101-42--1020;
NDC 002-3101-25--25; NDC 002-3101-50--50
NDC 002-3101-33--10100

[NOTE TO FIRM: Please include in your submission of final printed labeling, definitive descriptions of your packaging sizes that you intend to market, as indicated by your NDC designations. Additionally, please include in this section of the labeling, a description of appropriate storage conditions for your drug product.]

ANIMAL PHARMACOLOGY and/or ANIMAL TOXICOLOGY:

Monkeys treated with CESAMET at doses as high as 2mg/kg/day for a year experienced no adverse events of significance. This result contrasts with the findings in a planned one year dog study that was prematurely terminated because of deaths associated with convulsions in dogs receiving as little as 0.5mg/kg/day. The earliest deaths, however, occurred at 104 days in dogs receiving 1mg/kg/day. The unusual vulnerability of the dog to CESAMET is not understood; it is hypothesized, however, that the explanation lies in the fact that the dog differs from other species in its metabolism of CESAMET.

*Identi-Dose[®] (unit dose medication, Lilly)

END DRAFT LABEL

Please note that your application is considered approvable on the condition that a 24-month expiration date is utilized. Extension of the expiration date is dependent upon the receipt and review of the in vivo bioavailability study on aged formulations discussed in your June 28, 1985 amendment.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the revised draft labeling, further revision of the labeling may be required.

Finally, we request that you amend your application to include appropriate patent information as now required by the Act under Sections 505(b) and 505(c)(2), as amended by the "Drug Price Competition and Patent Term Restoration Act of 1984".

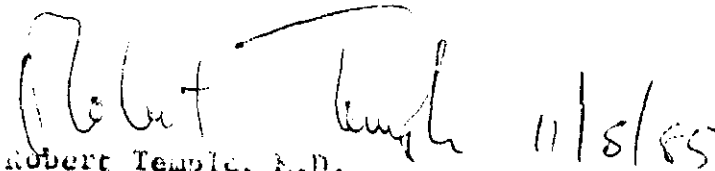
Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign; submit one copy to the Division of Neuropharmacological Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. We request that your proposed materials be submitted in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

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

Please submit twelve copies of the printed labels and other labeling.

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

Sincerely yours,

 11/8/85

Robert Temple, M.D.

Director

Office of Drug Research and Review
Center for Drugs and Biologics

SBA

SUMMARY BASIS OF APPROVAL

NDA 18-677

Applicant:

Eli Lilly and Company
307 East McCarty Street
Indianapolis, Indiana 46285

Drug Generic Name:

Nabilone

Drug Trade Name:

CESAMET

I. Indications for Use:

CESAMET Pulvules (Capsules) are indicated for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. This restriction is required because a substantial proportion of any group of patients treated with CESAMET can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents.

Because of its potential to alter the mental state, CESAMET is intended for use under circumstances which permit close supervision of the patient by a responsible individual.

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Evidence supporting the efficacy of CESAMET in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from both active-controlled (prochlorperazine) and placebo-controlled trials. Persuasive evidence was obtained in subjects being treated with a wide variety of chemotherapy regimens, including low dose cisplatin (20 mg/M²).

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

The usual adult dosage is 1 or 2 mg b. i. d. On the day of chemotherapy, the initial dose should be given 1 to 3 hours before the oncolytic agent is administered. To minimize side effects, it is recommended that the lower starting dose be used and that dose be increased as necessary. A dose of 1 or 2 mg the night before may be useful. The maximum recommended daily dose is 6 mg given in divided doses t. i. d.

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CESAMET may be administered 2 or 3 times daily during the entire course of each cycle of chemotherapy and, if needed, for 48 hours after the last dose of each cycle of chemotherapy.

III. Manufacturing and Control:

A. Manufacturing and Controls

The new drug substance is synthesized at Eli Lilly and Co. from commercially available chemicals using well established addition, reduction, and hydrolysis reactions with isomerization of the synthesized ketone to obtain the desired isomer.

Specifications and tests used in the manufacture and control of the new drug substance, inactive components and dosage strengths are adequate to assure identity, strength, quality and purity of the drug product. In addition to the usual physical tests, nabilone capsules are assayed by gas chromatography and thin layer chromatography is used for identification. The use of a surfactant in the dissolution test media assures that the more active bioavailable form of the drug substance is actually present in the drug product.

B. Stability Studies

The stability data supports a two-year expiration dating for the capsule dosage strengths in the proposed containers.

C. Methods Validation

The Division of Drug Chemistry (HFN-420), Washington, D.C. and the Detroit District (HFR-5360) laboratories validated the analytical methods and found them satisfactory for regulatory purposes. However, a few minor changes were recommended by the validating laboratories to assure that any future surveillance of the drug product would be consistent with that of the applicant.

D. Labeling

The immediate container labels, cartons and package insert bear satisfactory technical information. The proprietary name, CESAMET, does not appear to conflict with approved drug product names and the drug product is labeled as a Schedule II controlled drug.

E. Establishment Inspection

A statement from the Manufacturing Review Branch (HFN-322), Division of Drug Manufacturing, dated April 11, 1983, indicates that the facilities of Eli Lilly & Co., who manufacture the new drug substance and dosage form, are in compliance with current Good Manufacturing Practices.

F. Environmental Impact Analysis Report (EIAR)

The applicant includes a statement of exemption from complete reports on the basis of the small quantities involved and conformance with Federal, State and Local emission requirements which is acceptable.

IV. Pharmacology:

- A. Nabilone is related chemically to the naturally occurring cannabinoids, but differs by the presence of a 1,1-dimethylheptyl side chain and a keto group in the 9- position. Nabilone has been evaluated as an antiemetic for use during cancer chemotherapy and is believed to be a centrally acting antiemetic.

Pretreatment with nabilone reduced the emetic effect of the antineoplastics carmustine and mechlorethamine in cats. Nabilone was reported to be more effective than prochlorperazine in reducing cisplatin induced emesis in pigeons. Nabilone at doses up to 0.034 mg/kg i.v. was not effective in reducing apomorphine induced emesis in dogs. Prochlorperazine blocks this type of emesis presumably by its action on central dopamine mediated processes that is not shared by nabilone.

- B. In addition to acute toxicity studies in mice, rats, dogs and monkeys, the following subacute and chronic toxicity studies were submitted.

<u>SPECIES</u>	<u>ROUTE</u>	<u>DURATION/DOSE</u>
Rats	i.v.	14 days at 0 and 0.8 mg/kg/day
Rats	p.o.	92 days at 0, 6.25, 12.5 and 25 mg/kg/day
	p.o.	92 days at 0, 0.15, 0.62 and 2.5 mg/kg/day
Dogs	p.o.	92 days at 0, 0.25, 0.5 and 1.0 mg/kg/day
	p.o.	204 days at 0, 0.5, 1.0 and 2.0 mg/kg/day
Monkeys	p.o.	1 year at 0, 0.1, 0.5, and 2.0 mg/kg/day

The major effects observed in these studies were hypoactivity and sedation, especially during the first few days of dosing. Continued treatment led to apparent development of drug tolerance. Anorexia was also observed with the associated general reduction in growth and body weight gain as compared to controls.

Among the species used in chronic toxicity testing, dogs were most severely affected by nabilone. In particular, a planned one year study was terminated prematurely at 204 days because of increased mortality associated with severe convulsions. The incidence of mortality is apparently dose related (see Table I).

Table 1
Frequency of Convulsions and Mortality in Dogs
Treated with Nabilone IPF 204 days

<u>Dose mg/kg/day</u>	<u>No. of deaths preceded by convulsions/total number of dogs in each group</u>	<u>Total number of deaths/total number of dogs in each group</u>
0	0	0
0.5	2/8	2/8
1.0	4/8	6/8
2.0	3/8	7/8

In the 204 day dog study the earliest convulsion related death occurred after 104 days at 1 mg/kg/day of nabilone orally. An additional dog chronic toxicity study of 92 days in length produced no mortality or convulsions at doses up to 1 mg/kg/day, suggesting that the injury occurs only after a relatively long latency.

To determine if the convulsive effect of nabilone in the dog was peculiar to this species, a one-year chronic toxicity study was carried out with rhesus monkeys. The monkeys were dosed at 0, 0.1, 0.5, and 2.0 mg/kg/day of nabilone via nasogastric intubation. No treatment related convulsions or mortality was reported. The convulsions and death observed in the 204 day dog study therefore appear to be species related and associated with a cumulative effect of nabilone in the dog.

Why the dog is vulnerable to nabilone is not understood; perhaps an explanation lies in the manner in which the dog metabolizes nabilone. Carbinol metabolites produced by the enzymatic reduction of the 9-keto group of nabilone are major metabolites in the dog but are minor metabolites in humans and monkeys.

Fertility, reproduction and teratology studies in rats and rabbits demonstrated a maternal dose related decrease in food consumption and weight gain linked to a decrease in litter size and an increase in the number of stillborn pups, especially in high dose groups (12 mg/kg/day in the rat and 3.3 mg/kg/day for the rabbit). In perinatal and postnatal studies in the rat at 12 mg/kg/day, mean litter size and pup survival was significantly lower than controls. A cross-fostering study demonstrated that part of the detrimental effect of nabilone on neonatal survival was due to nutritional deprivation of the pups resulting from a reduction of milk production in the mothers. The reduction in milk production is apparently linked to the inhibitory influence of nabilone in prolactin release. Hypothermia was also a characteristic of offspring from nabilone treated females, which may be the result of both poor postpartum nutrition and some prenatal influence of nabilone. Nabilone was not associated with teratogenic effects in the rat or rabbit at doses more than 150x greater than that proposed for human use.

Nabilone is not genotoxic as judged by the results of the Ames test, sister chromatid exchange in the bone marrow of Chinese hamsters, dominant lethal studies in rats and the micronucleus test.

The toxicity and pharmacology of nabilone has been sufficiently described to support its safety and efficacy only for short term use in the control of nausea and vomiting caused by cancer chemotherapeutic agents. Any extension of its use as an antiemetic or for any other indication will require additional chronic toxicity testing and the completion of carcinogenicity testing.

V. Medical:

A. Background

After initial Phase I testing, nabilone was evaluated in approximately 70 patients for anxiolytic activity. Results were not encouraging, presumably because of dysphoric psychological effects associated with its use. However, reports of marijuana's antiemetic activity led the sponsor to evaluate nabilone as a treatment for cancer chemotherapy-induced nausea and vomiting. Nabilone's development as an antiemetic was interrupted in 1979 by the unexpected finding of convulsions and deaths in the one year dog toxicity test (see Pharmacology Section, above). Testing was resumed when studies revealed that monkeys treated at doses as high as 2mg/kg for a year did not suffer any convulsions or fatalities.

Data bearing on the safety of nabilone have been collected in controlled and open studies involving 978 patients. Assessments in these studies included: 1) clinical laboratory determinations (serum chemistry and hematology); 2) blood pressure; and 3) treatment emergent side effects.

Additional experience on nabilone's use as an antiemetic is available from post marketing experience in Canada (since 1982) and the United Kingdom (1983).

The abuse potential of nabilone has been assessed in 3 independently conducted studies. In these studies, nabilone was compared to delta-9-tetrahydrocannabinol (dronabinol). In one study, nabilone was compared to both delta-9-tetrahydrocannabinol and marijuana.

The conclusion that nabilone is an effective antiemetic is based upon reports of the four adequate and well controlled clinical studies involving nabilone that have been submitted to the NDA. In two studies, Protocol 9 and Protocol 28, nabilone was found to be superior to the control treatments employed (prochlorperazine and placebo, respectively), a result that provides persuasive evidence of efficacy. In the other two adequate and well-controlled studies,

Protocols 7 and 20, the effects of nabilone could not be distinguished from those of the active control treatment, prochlorperazine. Consequently, the results of these latter two studies can only be considered supportive of efficacy.

The individual adequate and well-controlled investigations are discussed below.

B. Well-Controlled Studies Demonstrating Effectiveness

1. Single-Center Study: Nabilone vs. Prochlorperazine, (Protocol #9)

a. Design:

This was a double-blind, randomized, two-period crossover comparison of the antiemetic effects of nabilone versus prochlorperazine in the treatment of nausea and vomiting associated with two consecutive, uniform cancer chemotherapy cycles. The treatments were usually 2 to 4 weeks apart. Nabilone or prochlorperazine was administered 30 minutes prior to chemotherapy to the first 60 patients enrolled; thereafter, patients received the study drug beginning the night before starting chemotherapy and throughout the 1- to 5-day treatment courses. The usual dose was 2 mg nabilone, every 6 hours as needed or 10 mg prochlorperazine every 6 hours as needed.

Ninety-eight (98) patients (83 male, 15 female), aged 15 to 74, were enrolled in the trial. Eighty-three (83) patients completed both arms of the crossover without protocol violations (e.g., administration of second antiemetic agent, study drug not administered 1 to 3 hours prior to chemotherapy, etc.) The majority (68) of the 83 completers had testicular cancer for which they received the following chemotherapy regimen: 5 days of cisplatin (20 mg/M²) and 1 or 2 days of concurrent therapy with bleomycin, vinblastine or adriamycin.

b. Efficacy parameters and safety monitoring:

Patients rated study drug effect on vomiting frequency, nausea severity and food intake. Vomiting frequency was recorded on a 24-hour basis. Nausea was graded daily on a 0 to 3 scale with 0 equaling no nausea and 3 equaling severe nausea. Food intake was also graded daily on a 0- to 3-point scale equaling "none" to "more than usual." Patients were additionally asked to compare treatments in terms of perceived relative efficacy.

Safety assessments included a physical examination with clinical laboratory determination [hematology and blood chemistry (SMA 12/60)] before and after each cycle of chemotherapy. Blood pressure and heart rates were obtained in patients after lying, sitting and standing. These determinations were made every 6 hours following study drug administration and for 12 hours following study completion. Adverse reactions were to be noted by both patients and investigators.

c. Results:

The results were analyzed by a non-parametric analysis of variance for both the "parallel groups" first period and crossover portions of the study. Because many patients failed to complete the full cross-over, the analysis that treated the first period of the randomized cross-over as a parallel comparison of nabilone and prochlorperazine was used as the basis for conclusions about the study. This approach avoids the possible bias introduced by dropouts.

The analysis of first period results revealed a significant antiemetic effect favoring nabilone on day 1 vomiting ($p=.038$), average vomiting frequency ($p=.005$), and average food intake ($p=.022$). The critical outcome variables available in this study, severity of nausea and frequency of vomiting, are displayed in table 2.

Table 2
Protocol 9
Cycle 1, All Patients Analysis (non-parametric rank test)

	<u>Average Frequency of Vomiting</u>	<u>Average Severity of Nausea</u>
Nabilone		
Mean	3.11	1.33
S.D.	6.12	0.95
n	44	44
Prochlorperazine		
Mean	6.02	1.64
S.D.	7.50	0.84
n	43	43
P-value	.005	.090

In addition to the 98 patients enrolled in the efficacy analysis, two additional patients were admitted directly to open label nabilone. Fifty-two (52) of 96 patients (54.2%) continued on an open label basis. All were included for evaluation of safety.

Five (5) patients discontinued nabilone because of adverse experiences. None discontinued after a 1 mg dose. One (1) discontinued after a single 2 mg dose and two after 4 mg. One patient took 3 days of drug (14 mg). All discontinued because they did not "like" the feeling. Ninety six (96) patients received at least one dose of nabilone. Of this group, 90/96 (93.8%) reported at least one adverse experience; 74/92 (80.4%) taking prochlorperazine reported at least one adverse experience. The most common adverse experiences related to nabilone administration were drowsiness, vertigo and a "high"; 3 patients experienced orthostatic hypotension and one had syncope. Blood pressure recordings were incomplete in most patients but most had more than one blood pressure recorded in each cycle. Significantly greater decreases of blood pressure (systolic-standing p-value less than .001, diastolic standing p=.004) were observed on nabilone.

The incidence of side effects approached 100%. Of those who received drug, 70% continued to receive it through day 5.

d. Conclusions:

This study provides strong evidence of effectiveness. In this experiment, the average outcome of patients on nabilone, as judged by severity of nausea and frequency of vomiting, is superior to the outcome of patients assigned to prochlorperazine, an established antiemetic drug product.

The results also permit the inference that nabilone can reduce the nausea and vomiting induced by treatment with cisplatin in combination with bleomycin, vincristine or adriamycin.

Finally, the study illustrates that the antiemetic/antinauseant activity of nabilone is accompanied by a high incidence of troublesome adverse effects. Indeed, the vast majority of patients experienced at least one adverse effect; drowsiness, vertigo and "high" were most common. There is a suggestion, however, that patients may differ in the degree of their willingness to tolerate nabilone related untoward effects. Dropouts generally occurred early during a course of treatment or not at all. A 1 mg dose did not lead to any dropouts but three-quarters of the dropouts had received a maximum of 4 mg of the drug. Those who did not drop out initially remained in the study and most received 5 days of treatment.

Of the 96 patients who received at least one dose of nabilone, 10 (10.4%) received an average daily dose of 2 mg or less, 35 (36.5%) received a daily dose of between 2 and 4 mg, and 51 (53.1%) received a total daily dose of at least 4 mg. The incidence of side effects in these 3 groups was 90%, 91.4%, and 96.1% respectively.

2. Multicenter Study: Nabilone vs. Placebo (Protocol # 28)

Six investigators participated in the trial:

A routine inspection of one of the investigators revealed multiple, serious IND regulation and protocol violations. For these reasons, the study was analysed excluding the data provided by this investigator.

a. Design:

This was planned as a double-blind, randomized, placebo-controlled two-period crossover study of nabilone in cancer patients undergoing 2 consecutive, uniform chemotherapy cycles with agents known to produce nausea and vomiting. The order of administration was counterbalanced. The study drug (nabilone or placebo) was administered the evening prior to the initiation of chemotherapy and then twice a day throughout the chemotherapy cycle. The unit dose of nabilone was 2 mg. Cycles were usually 3 to 6 weeks apart.

In order to participate, male or female cancer patients had to be at least 16 years old, give informed consent, and have a treatment that was expected to be the same over two consecutive chemotherapy courses. Patients could have been excluded for any of the following reasons: (1) receiving high dose cisplatin (100 mg/M²/day); (2) pregnancy; (3) not using contraception; (4) clinically significant hepatic, renal or CNS disease; (5) psychosis; (6) progressive disease of the eyelids; (7) a body weight of less than 45 kg; (8) alcohol or drug addiction, (9) or use of other psychotropic drugs, including marijuana, during the study.

b. Efficacy parameters and safety monitoring:

Patient rated efficacy variables were vomiting frequency, severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual, more than usual). Each

variable was rated over a 24-hr period. At the end of the 2 cycles, patients were asked to rate their preference (nabilone better, same, placebo better) on the variables.

Investigators rated global efficacy (very good, good, fair, poor, very poor) and a global impression of adverse effects on patient's ability to function (none, did not interfere with patient's functioning, significantly interfered with patient's functioning, and "outweighed the therapeutic effect".)

Safety assessment included a medical history, physical examination and clinical laboratory determination [hematology (hemoglobin, hematocrit, reticulocyte count, platelet count, and differential); SMA 12/60; and urinalysis] at baseline. All laboratory measurements were to be repeated at termination or discontinuation. Blood pressure and pulse rates were to be obtained within one week of each chemotherapy cycle and after completion or discontinuation. Patients were to be monitored for postural hypotension at 3 to 4 hours after the morning dose of study medication, where feasible. Both supine and standing blood pressures were to be determined.

Adverse reactions were noted by both patients and investigators. The investigator was asked to rate adverse reaction severity.

Statistical analysis was performed to identify significant differences in treatment variables (prior chemotherapy, type of chemotherapy) and patient demographics (sex, age).

A non-parametric analysis of variance was performed by the sponsor on patient and investigator rated data from individual investigators. Additionally, an analysis of variance of the composite (6 center) data was undertaken. The agency relied on the analysis of the first period data, rather than the crossover data, for reasons previously stated. A categorical analysis was performed on patient-rated variables and drug preference as well as investigator-rated variables.

Blood pressure data were analyzed for changes (increase vs. decrease) in systolic and diastolic pressure within treatments on an investigator and a composite basis. Data were also analyzed for magnitude of the pressor or depressor effects between treatments on patients who completed both periods. This analysis was performed on both an investigator and a composite basis. The Chi-Square test was used to assess significant differences.

c. Results:

Because one investigator's data was excluded from consideration in this study, the sponsor's analysis of the pooled data was not used, and the agency reanalyzed the pooled data, omitting the

data from the excluded study. This analysis revealed statistically significant effects favoring nabilone on global efficacy and severity of nausea. In addition, there was a marginally significant ($p = .07$, 2 tailed) difference in favor of nabilone for frequency of vomiting.

Table 3
Pooled Results on Protocol 28
(less excluded center)
(nonparametric rank analysis)

<u>Drug</u>	<u>Average Frequency of Vomiting</u>	<u>Average Severity of Nausea</u>	<u>Global Impression</u>
Nabilone			
mean	6.26	1.53	2.45
n	58	58	58
Placebo			
mean	15.1	2.12	3.62
n	65	65	65
P-value "2-tail"	p=0.07	p less than 0.01	p less than 0.001

Furthermore, an analysis of patient preference (calculated by assigning patient preference to the alternate therapy for those patients who did not complete the cross-over due to adverse reactions or lack of efficacy) revealed that 82 patients preferred nabilone to 32 preferring placebo, a highly significant finding.

d. Conclusion:

This study provides persuasive evidence of the efficacy and safety of nabilone as an antiemetic.

C. Well-Controlled Studies Supporting Effectiveness

1. Multi-Centered Study: Nabilone vs. Prochlorperazine (Protocol #20)

a. Design:

This study was conducted at three sites:
(Investigator 301); (Investigator 302);
(Investigator 306). The study
was interrupted in January, 1979 after 10 patients had
enrolled.

This was a double-blind randomized, two-period crossover comparison of the antiemetic effects of nabilone versus prochlorperazine in the treatment of nausea and vomiting associated with two consecutive uniform chemotherapy cycles. Treatment cycles were usually 3 to 6 weeks apart.

Nabilone (2 mg) or prochlorperazine (10 mg) were administered the evening before chemotherapy and then twice a day for the duration of the chemotherapy cycle. The prochlorperazine dose is an effective although less than optimal dose, but results were evaluated on the basis of nabilone's superiority to the prochlorperazine dose regimen.

Of the 126 patients who entered the trial, 75 (60%) were considered evaluable. There was considerable diagnostic heterogeneity of the treatment groups among the three centers. The data from this study were analyzed both by investigator/site and as a composite.

b. Efficacy parameters and safety monitoring:

There were three patient-rated efficacy variables: vomiting frequency, nausea severity (0 to 3 scale equal to none to severe), and food intake (0 to 3 scale equal to "none" to "more than usual"). Patients also rated each variable at the end of the trial as to which drug was better, if either. Patients were also asked to choose an overall drug preference.

Investigators rated global efficacy on a 5-point scale (1 to 5 equaling very poor, poor, fair, good, and very good) and judged adverse effects on a 0 to 3-point scale (none, did not interfere with patient's functioning, significantly interfered with patient's functioning, and outweighed the therapeutic effect).

Safety assessment included a physical examination with laboratory determinations (hematology, SMA 12/60, and urinalysis) prior to each cycle of chemotherapy, and after completion of the crossover. Patients were asked to note treatment emergent reactions on a daily questionnaire.

Blood pressure changes were assessed on inpatients at pre-drug and 2 hours post-drug administration. Outpatients were to be monitored if they remained in a treatment setting.

Statistical analysis was performed on data generated from individual investigators and the composite of the three centers. The major analysis was a non-parametric analysis of variance on the ranked data. Secondary analyses included a categorical analysis of patient and investigator judgments on

which treatment was better on the efficacy parameters and side effect severity. The crossover study was also collapsed into a parallel groups analysis of all patients receiving a study drug (nabilone or prochlorperazine) during the first period. As with the other studies, the agency relied on the analysis of the first period to determine nabilone's effects.

c. Results:

(Investigator #301) enrolled sixty-seven (67) patients, 43 male and 24 female, between the ages of 19 and 58 years old in the study. The largest treatment group was lung cancer patients (45%), followed by melanoma (9%), bladder (7%), colon (7%) and testicular (7%) cancers. Thirty-two (32) of the 67 enrollees were considered evaluable. Thirteen of those considered unevaluable were administrative terminations at the time of suspension of the nabilone clinical trials. Thus, 54 patients received at least one dose of either study drug.

The most common cancer chemotherapy regimen was cisplatin in combination with vindesine in the treatment of lung cancer. Cisplatin therapy was categorized as being above or below 100 mg/M². Thirteen of the high dose (greater than or equal to 100 mg/M²) and 8 of the low dose (less than 100 mg/M²) cisplatin group completed both periods of the crossover.

(Investigator #302) enrolled forty-nine (49) patients, 39 male and 10 female, between the ages of 17 and 64 years old at this site. The largest treatment groups were 32 testicular cancer patients followed by 7 breast cancer patients. Thirty-six (36) patients were considered evaluable. Of this group, 23 received cisplatin and other drugs in combination for their chemotherapy regime.

The most common chemotherapy for testicular cancer was a 5-day course of cisplatin (20 mg/M²). Bleomycin and vinblastine were usually only administered on day 1 of the treatment cycle. Breast cancer patients were treated with Adriamycin, cyclophosphamide and 5-fluorouracil. Patients treated with cisplatin did not have to meet the criterion of two previous, consecutive vomiting episodes.

(Investigator #306) enrolled ten (10) patients, 4 male and 6 female, between the ages of 23 and 78 years old in this study prior to the administrative termination of this multicentered trial. Seven (7) patients were considered evaluable. This group was comprised of 2 breast cancer patients, 2 connective tissue and mesothelioma patients, 2 lymphoma patients, and 1 adenocarcinoma patient.

A comparability analysis demonstrated the heterogeneity of the patient and treatment variables across the three investigative sites; i.e., statistically significant differences (p-value less than or equal to .05) were found for age and sex of the patients, type of chemotherapy and prior chemotherapy. Additionally, a significant investigator by evaluability interaction was noted; i.e., the proportion of evaluable patients significantly differed across the three investigators.

The data analyses for the composite study were the same type as those performed on the individual sites. However, appropriate interaction variables had to be factored into the analysis.

The analysis of the combined first period "all patients" group effects showed an investigator by treatment interaction for day 1 vomiting frequency (p=.046). There were no significant differences between nabilone and prochlorperazine with respect to the patient-rated treatment variables, although nabilone was favored. A significant advantage for nabilone was found for the investigator's global impression (p-value less than .001). Adverse effects were also more severe in the nabilone group (p=.002).

Table 4
 Protocol 20, all subjects analysis
 cycle 1 (parallel comparison)
 Non-parametric Rank Analysis

<u>Drug</u>	<u>Average Frequency of Vomiting</u>	<u>Average Severity of Nausea</u>	<u>Global Impression</u>
Nabilone			
mean	8.00	1.55	2.25
n	53	59	56
Prochlorperazine			
mean	10.53	1.83	3.12
n	44	52	52
P-value "2-tail"	NS	NS	p=0.047
(lower scores are more favorable)			

d. Conclusions:

This well-controlled study provides supportive evidence of the antiemetic superiority of nabilone over prochlorperazine in patients receiving cancer chemotherapy. The combined analysis fails to demonstrate a difference between nabilone and prochlorperazine. However, the study populations were different at the two study centers () that provided the bulk of the evaluable data. The patient populations in these two centers exhibited considerable diagnostic heterogeneity across centers and, consequently, chemotherapy regimens varied across centers. The major chemotherapy difference noted was the dose of cisplatin, being 100 mg/M² in the () study and 20 mg/M² in the () study. Nabilone was equal to prochlorperazine in the () study and superior to prochlorperazine in the () study. These data suggest that nabilone may be relatively more efficacious against lower doses of cisplatin.

One hundred and eleven (111) patients received nabilone. The rate of adverse reactions was approximately 80%. Patients dropped out most commonly following a single 2 mg dose of drug. If they passed the first 1 or 2 doses they generally tolerated the drug thereafter. The rate of adverse reactions was considerably lower on prochlorperazine (average 43.6%) and adverse reactions were dose-related. Blood pressure data were grossly incomplete (75/126 had only one blood pressure follow up) and the true incidence of symptomatic hypotension is therefore likely underreported. Incidence of adverse reactions less than 5% were not recorded.

2. Single-Center Study: Nabilone vs. Prochlorperazine (Protocol 7)

a. Design:

This was a double-blind, randomized, two-period crossover study comparing the antiemetic effects of nabilone versus those of prochlorperazine in the treatment of chemotherapy induced nausea and vomiting during two consecutive, uniform chemotherapy cycles. The order of study drug administration was counterbalanced. The study drug (nabilone or prochlorperazine) was administered the evening before chemotherapy and continued throughout chemotherapy. Dosing with nabilone varied and ranged from 1 to 6 mg/day. Prochlorperazine doses ranged from 10 to 30 mg/day.

Criteria for study participation were that cancer patients aged 17 to 70, had to have experienced severe nausea and vomiting with previous courses of chemotherapy. Pregnant women and patients with severe atherosclerotic vascular disease were excluded.

b. Efficacy parameters and safety monitoring:

Efficacy parameters consisted of 3 patient-rated variables: vomiting frequency, nausea severity (none, mild, moderate, severe), and food intake (none, less than usual, usual, more than usual). The investigators also rated the quality of the antiemetic response in evaluable patients. Three categories were used: (1) complete - no nausea or vomiting; (2) partial - equal to greater than a 50% reduction in nausea and vomiting; and (3) none - less than a 50% reduction in nausea and vomiting.

Safety evaluation consisted of a medical history, routine hematology and SMA 12/60 on each patient prior to each study drug period and at termination. Adverse reactions were recorded by the patients. The investigator was asked to judge whether adverse effects were study drug-related.

Patients were considered evaluable if they completed at least one day on both cycles without a protocol violation. Violations were considered to be as follows: (1) a second antiemetic, including marijuana, given or used by the patients; (2) a study drug was not given concomitantly or as specified by the study protocol; and (3) a different chemotherapy regimen was instituted in the second chemotherapy cycle.

Statistical analysis consisted of the non-parametric analyses of variance on patients completing the two-period crossover and the parallel groups analysis of all patients in the first period. Categorical analysis was performed on the patient-rated variables (nabilone better, same, prochlorperazine better).

Blood pressure changes were analyzed for direction of change within drug therapy and magnitude of change between drug therapies.

In addition to the sponsor's analysis, the investigators analyzed the "quality of antiemetic response" using test. They also analyzed vomiting frequency data using the sign test.

c. Results:

Forty-three (43) patients, 18 male and 25 female, enrolled in the study. Twenty-nine (29) patients, aged 17 to 70, were considered evaluable in the sponsor's analysis; 33 patients were considered evaluable in the investigator's analysis.

The most frequent chemotherapy treatment used a combination of bleomycin, nitrogen mustard, procarbazine and Vincristine in patients with Hodgkins's disease (n = 13 patients). Four of the 29 evaluable patients received cisplatin-based regimens.

Both the parallel groups comparison and the categorical analysis of the first period failed to show any treatment-related differences on the efficacy variables in the sponsor's analysis (data not shown).

All 43 patients received at least one dose of nabilone. Five patients terminated early due to nabilone-related side effects, most after a single 2 mg dose.

One patient who received nabilone discontinued because of orthostatic hypotension with syncope. Four additional patients were found in whom drug effects led to dropout. All of the 43 patients on nabilone reported at least one adverse reaction.

d. Conclusions:

This well-controlled study provides supportive evidence of the antiemetic efficacy of nabilone against chemotherapy-induced nausea and vomiting. Nabilone's antiemetic activity was equivalent to that observed in the prochlorperazine group.

All patients experienced at least one adverse event. There was a single dropout due to orthostatic hypotension. The remaining dropouts complained of the more common dizziness, dry mouth and "high", confusion and occasionally euphoria.

The findings of CNS and cardiovascular side effects are in agreement with the other studies.

D. Overall Effectiveness Summary and Conclusion

The effectiveness of nabilone as an antiemetic drug for chemotherapy-induced emesis has been demonstrated in an active control trial (Protocol # 9) and the multicenter placebo-controlled trial (Protocol # 28). Further support of efficacy was obtained in Protocols # 7 and # 20, in which the antiemetic effect of nabilone was equivalent to that of prochlorperazine. Nabilone appears to be effective against low dose (20 mg/M²) cisplatin-based regimens as well as noncisplatin-based regimens.

The usual dose of nabilone is 2 mg twice daily. Dosing should be initiated the evening before chemotherapy and may continue for 24 to 48 hours post-chemotherapy.

Because the positive results obtained in three of the four adequate and well controlled clinical investigations are heavily dependent on the results of one investigator, it was important to examine the efficacy data to ensure that evidence of nabilone's efficacy was available from more than one source; i.e., to determine whether the NDA provided 'replicated' and independent evidence of efficacy.

Several approaches to the problem are possible. One was to analyze the results of multicenter Protocol 28 excluding the Einhorn data. Our results utilizing "all patients cycle 1" analyses produced two-sided p-values less than .05 for frequency of vomits, severity of nausea, and global impression. Another was to examine the outcome of individual centers in Protocol 28 to determine whether or not additional centers corroborated result. Two studies were of sufficient size to permit independent analysis. One, (Inv. # 006) provides independent confirmation of finding.

This study was still in progress at the time of NDA submission. At that time, 45 patients (20 males and 25 females) were enrolled in the study. Thirty-six patients (16 males and 20 females), average age of 56 years, were considered evaluable. Four of the dropouts sustained an adverse reaction to nabilone. Two other dropouts reported a lack of efficacy with placebo as a reason for not completing the crossover. Two other terminators decided not to continue. One death was reported during the study. This patient's death was disease-related.

Of the 36 evaluable patients, 11 had breast cancer and 8 had lung cancer. The most common treatments for these cancers was adriamycin in combination with 5-fluorouracil, cyclophosphamide and methotrexate. Eight study completers received cisplatin-based regimens. In all patients, the chemotherapy regimens lasted only 1 day.

The results of the "all patients cycle 1" analysis are in general agreement with the analysis of variance in the two-period completers. There was a trend toward nabilone superiority on day 1 vomiting ($p=.083$). Nabilone's superior anti-nauseant and mild appetite stimulation effects reached statistical significance. The investigators rated nabilone as more efficacious with a mild-to-moderate adverse effect on patient's global functioning.

Table 5
Protocol 28, Analysis of
Investigator # 006
cycle 1 (parallel comparison)
Non-parametric Rank Analysis

<u>Drug</u>	<u>Average Frequency of Vomiting</u>	<u>Average Severity of Nausea</u>	<u>Global Impression</u>
Nabilone			
mean	5.48	1.26	2.48
n	21	21	21
Placebo			
mean	9.13	2.00	3.52
n	20	21	21
P-value "1-tail"	0.140	0.017	0.005

The results of the categorical analysis (data not shown), in general, support the analysis of variance. In this analysis, nabilone was clearly a superior anti-nauseant and increased food intake.

Of 41 patients who received at least one dose of nabilone, 4 terminated early due to the adverse experiences with nabilone. Seventy-eight per cent (78%) had at least one adverse drug experience. Blood pressure records were not available for every patient.

Conclusions of Study Center 006: This well-controlled study provides persuasive evidence of the antiemetic superiority of nabilone over placebo. In this study, a greater anti-nauseant effect was found. This may be due to the possibility that the majority of the chemotherapy regimens induced a greater nausea effect relative to their emetogenic effects.

The dropout rate (10%) and the adverse reaction rate (78%) for nabilone are consistent with those observed in other centers.

The analyses of "cycle 1" data from study show nabilone's superiority over placebo. This result provides independent corroboration for the findings of removing any substantive concern about a single source providing all evidence of efficacy.

E. Summary of Safety Data from Controlled Studies

The following tables compare the incidence of Adverse Reactions that occurred in the controlled studies described above:

Table 6
Incidence of Adverse Reactions in Protocol 28
(Data Removed)

<u>ADR</u>	<u>Nabilone</u> (n = 134)		<u>Placebo</u> (n = 119)	
	<u>Patients</u>	<u>Percent</u>	<u>Patients</u>	<u>Percent</u>
Vertigo	69	51	3	2.5
Drowsiness	69	51	6	5
Dry Mouth	47	35	2	1.7
Ataxia	19	14	0	0
Depersonalization	2	1.5	1	0.8
Euphoria	14	10.4	1	0.3
Sleep Disturbance	14	10.4	1	0.8
Dysphoria	12	9	0	0
Headache	8	6	0	0
Nausea	5	3.7	0	0
Disorientation	3	2.2	0	0

Table 7
Total Incidence of Adverse Reactions in
Active Controlled Studies, (Protocols 7, 9, and 20)

<u>ADR</u>	<u>Nabilone</u> (n = 250)		<u>PROCHLORPERAZINE</u> (n = 232)	
	<u>Patients</u>	<u>Percent</u>	<u>Patients</u>	<u>Percent</u>
Drowsiness	165	66	108	47
Vertigo	111	44	42	18
Dry Mouth	102	41	10	4
High	95	38	12	5
Concentration Difficulties	62	25	3	1
Dizziness	36	14	11	5
Depression	35	14	37	16
Ataxia	31	12	4	2
Headache	30	12	12	5
Visual Disturbance	30	12	9	4
Asthenia	20	8	4	2
Anorexia	19	8	22	9
Hypotension	17	7	2	1
Sedation	14	6	2	1
Increased Appetite	12	5	0	0

F. Additional Clinical Toxicity Experience with CESAMET

Studies in normal volunteers and other patient populations were evaluated in the overall safety assessment of nabilone. These studies include Phase I and Phase II dose-ranging studies, pharmacokinetic studies, early Phase II dose-ranging antiemetic studies, and studies in patients with anxiety disorders and glaucoma. These studies are summarized below.

1. Dose-Ranging Studies and Early Pharmacokinetic Studies:

(a) (Protocol 1)

A study in which three patients received single doses up to 5 mg, and 9 patients received single 2 mg doses.

Side effects were experienced at doses less than 3 mg; chiefly lightheadedness, dizziness, drowsiness, euphoria, dry mouth. One subject (1/9) had documented postural hypotension. At doses less than 3 mg there were no significant findings. At doses above 3 mg all subjects had dry mouth and euphoria. At 5 mg all complained of dizziness, postural hypotension and slight tachycardia. It is interesting that one subject described a "high" on placebo on at least 2 occasions.

(b) (Protocol 2)

Three (3) subjects participated in this multiple dose tolerance study in normal volunteers. Nabilone was administered to one patient in a dose of 1 mg twice daily for 7 days. Symptoms reached a peak in the 2nd day and disappeared on day 4. The dose was increased to 2 mg twice daily for 7 days, and again tolerance developed. Two out of 3 of the study subjects developed mild postural hypotension.

A 5 mg challenge dose was given after 7 days of treatment and only a mild increase in symptoms occurred. After one week off drug, a 5 mg dose produced marked side effects. No signs of abstinence accompanied withdrawal.

(c) Part I (Protocol 7)

Thirteen (13) patients who had experienced severe nausea and vomiting associated with parenteral cancer chemotherapy and who had been resistant to treatment with prochlorperazine were randomized to receive either 1 mg or 2 mg three times daily of nabilone 30 minutes prior to chemotherapy. Toxicity was rated as mild, moderate or severe.

Dizziness, decreased coordination, drowsiness and dry mouth were most common. Three (3) patients had severe reactions at each dose. The investigators stated that a feeling of dissociation tended to persist 2 to 3 days after nabilone was discontinued. Dose made no apparent difference in either effect or toxicity. Most patients experienced side effects - none serious.

(d) (Protocol 3)

Eight (8) patients received a single intravenous dose of either 0.25 mg, 0.5 mg or 1 mg. The 1 mg dose was followed by marked side effects.

One subject after 1 mg described emptiness, euphoria, restlessness, numbness, drowsiness and epigastric distress. The change in sensorium lasted 24-36 hours. One subject experienced postural hypotension, dizziness, tachycardia, drowsiness, headache, fatigue and euphoria.

(e) Protocol 5)

Oral ¹⁴C nabilone was administered in a single oral dose of 2 mg in 2 subjects.

Postural hypotension, dizziness, headache and general malaise were reported in the 2 subjects.

(f) (Protocol 30)

Bioavailability study: Deuterated capsules of nabilone suspension 2 mg were administered to 4 males in different formulations. All experienced dry mouth. Drowsiness, and "high" were also seen.

(g) (Protocol 35)

Dose Proportionality Study: This was a four-way crossover study of various formulations with a maximum dosage of 3 mg (p.o.). All 4 subjects experienced adverse reactions, including dry mouth, dizziness, and drowsiness.

2. Antianxiety Studies:

This protocol was originally planned to apply to healthy volunteer subjects 18-48 years of age, untreated for anxiety. They were recruited for high levels of state and trait anxiety based on Hamilton anxiety score, Hopkins Symptom Checklist, Self-Rating Symptom Scale and a Raskin-Cori Rating of 8.

One hundred fifty-seven (157) subjects (50 females and 107 males) were enrolled. In September of 1978 it was decided to discontinue the study of nabilone as an antianxiety agent because of hallucinations and altered mental state in patients who participated in antianxiety and antiemetic studies.

The reports, therefore, give safety data only, and are summarized below (Table 7):

Table 8
Anti-Anxiety Studies

Type	Controls	Investigator	Study No.	No. of Subjects	Nabilone Dose (mg)	Frequency
Crossover						
Single-Blind	Placebo		8	9	0.5-4.0	Q-WKx9**
Double-Blind	Placebo		10	12	1.0-2.5	b.i.d.
Parallel						
Dose-Ranging	None		12	5	1.0-4.0	b.i.d.
Double-Blind	Placebo		12	20	1.0	t.i.d.
Double-Blind	Placebo		121	8	1.0	t.i.d.
Double-Blind	+Diazepam*		14	45	1.0	t.i.d.
Double-Blind	Placebo		6	49	2.0	1 dose
Double-Blind	+Diazepam*		221	9	1.0	t.i.d.

*Diazepam dose was 5 mg per nabilone schedule

frequency matching the corresponding

**Doses were given once a week for 9 weeks

Of the patients enrolled 70 received nabilone.

There were no life-threatening events. The most frequently reported adverse experiences were dry mouth and drowsiness. No laboratory abnormalities were reported. Six (6) patients were considered dropouts due to adverse drug experiences. No control diazepam patients dropped out. One patient had previous drug addiction and alcoholism and developed an acute toxic encephalopathy thought to be secondary to an unprescribed drug, from which he recovered. Another patient had orthostatic hypotension not considered drug-related, and additionally experienced headache and nausea, which were considered drug-related, resulting in discontinuation of medication.

Three patients reported similar lightheadedness, confusion, headache, dry mouth and "high."

The reports of adverse experiences were separated into those considered drug-related and those which were not. This is in contrast to the other studies where these categories were combined. Therefore, the listed incidences should be combined

for comparison; e.g., dry mouth 21.4 and 8.6%, dizziness 4.3 and 2.9%. "High" is listed under CNS symptoms and was reported in 1.9% of patients. The symptoms were comparable to all other studies. However, in these studies dropouts occurred after many days of drug administration.

3. **Glaucoma Study:**

This study was discontinued. Seventeen (17) were enrolled and received drug. Five percent (5%) of the patients reported 78.9% of the adverse effects. Most received a single dose (2 mg); 5 patients received multiple doses. Five (5) serious effects were reported. All but one patient had their reactions after a single dose. In all, a significant blood pressure drop occurred (to 70/40, 60/40, 60/40/ 100/40) and one patient had clinical "orthostatic hypotension." One patient after a single dose was nauseous and fainted.

It is noteworthy that these patients were older than those in other studies (all but 2 were older than 58 years). The symptoms (excluding hypotension) were nausea, lightheadedness, drowsiness, dry mouth, faintness, giggling and vomiting. Most (12/17) reported minimal or no symptoms.

The most striking aspect of this study was the prominent hypotension in a group of older patients following one dose of drug.

4. **Open Label "Emergency Use" in Chemotherapy:**

Sixty (60) patients received nabilone on an "emergency basis" for treatment of nausea and vomiting during cancer chemotherapy. The drug was administered on an open label basis, 2 mg twice daily with the initial dose the night before chemotherapy. The adverse reactions of greater than 5% incidence were dizziness (15.3%), drowsiness (14.6%), and dry mouth (6.7%).

G. Abuse Potential Evaluation

1. **Background:**

A major issue that overlaps with traditional safety considerations is the abuse potential of a given psychotropic agent. The agency is charged with making medical/scientific determinations of a drug's potential for abuse for scheduling purposes under the Controlled Substances Act (CSA). Indeed, a recommendation from the Secretary of Health and Human Services to affect control of a drug under the CSA is considered legally binding on the Administrator of the Drug Enforcement Administration.

The chemical structure of nabilone places it in the loosely termed "cannabinoid" drug class. It is not known at this time whether therapeutic effects within the cannabinoid drug class can be effectively separated from the constellation of psychotropic effects that comprise the psychopharmacological effects of these agents. Nabilone is no exception to this concern. Indeed, in many instances in the clinical trials it was apparent that there is a subgroup of patients who can not tolerate the potent psychotropic effects of nabilone.

The CSA has four schedules for control of drugs with an approved medical use. This presupposes that drugs within a given pharmacologic or therapeutic class may exhibit a gradation of abuse potential and/or a differential capacity to affect physical or psychological dependence. In order to gauge the relative abuse potential of a given substance it must be compared to an appropriate standard(s). In the case of nabilone, it has been argued that either marijuana or delta-9-tetrahydrocannabinol (delta-9-THC) would be appropriate comparisons. The agency believes that the more relevant comparison is to evaluate nabilone vis a vis delta-9-THC. This implies that marijuana has more abuse potential than delta-9-THC.

The sponsor supported two clinical studies which contained comparisons between nabilone and delta-9-THC with respect to psychopharmacological effects. These studies are summarized below:

(1) (Protocol 31)

This study compared the physiologic, subjective and psychomotor effects of nabilone versus delta-9-THC in 6 male volunteers who were experienced marijuana smokers. Subjects received five different treatments in a randomized, double-blind manner. Each subject received placebo (oral and i.v.), nabilone (2 mg, p.o.) and placebo i.v., delta-9-THC orally (17.5 mg) and placebo i.v., placebo orally and nabilone (0.25 mg, i.v.), and placebo orally and delta-9-THC (2.2 mg, i.v.).

Subject's heart rates and blood pressures were monitored throughout the study. Subjective effects were assessed using the Cornell Medical Index (CMI) and an Addiction Research Center Inventory (ARCI) through the first 8 hours post-drug administration. Subjects were also asked to describe effects during each session. At the end of the five sessions, each subject was asked to rate drug preferences.

The following psychomotor tests were administered to all subjects in all experimental sessions, wobble board test (an indication of "balancing movements"), pursuit meter testing (measures attentive motor performance and hand-eye coordination), a delayed auditory feedback test (a measure of cognitive/mental performance), and a mirror drawing test (a measure of induced anxiety).

Results: Delta-9-THC (i.v.) produced the greatest increase in supine and standing heart rates. Nabilone's effect (i.v.) was qualitatively similar but of a lower magnitude.

Intravenous delta-9-THC and nabilone had a peak response at 1 hour on the CMI "high" score. No other statistically significant differences from placebo in CMI scores were seen. Subject preference for treatments in decreasing order was: THC (i.v.), nabilone i.v., nabilone oral, THC oral, placebo. However, differences between the active treatments were statistically different from placebo, but not from each other.

In the wobble test, i.v. delta-9-THC had the greatest effect on balance. These results were approximately equal to those observed with oral THC or i.v. nabilone. Interestingly, oral nabilone's peak effect in this test occurred at 4 hours, suggesting a different time course of peak "high" and psychomotor deficits.

No statistically significant effects could be detected in the pursuit meter test. However, when subjects were questioned about impaired driving ability the following positive responses were obtained: 5/6 i.v. THC, 4/6 i.v. nabilone, 4/6 oral THC, 2/6 oral nabilone and 0/6 placebo.

No other statistically significant differences occurred in the psychomotor tests.

Conclusions: In this study, a qualitative difference between nabilone and delta-9-THC was observed on heart rates. The subjective effects of nabilone and THC within routes of administration are nearly indistinguishable, suggesting that no meaningful differences in subjective effects could be found. Accordingly, inasmuch as the subjective effects predict relative abuse potential, nabilone and THC are equivalent in abuse potential. Further, inasmuch as the subjective effects of these equivalent cannabinoid drugs infer a relationship to the high psychological dependence capacity of cannabis drugs, the psychological dependence capacity of nabilone and delta-9-THC are equivalent.

(2)

(Protocol #33)

This was a randomized, double-blind, placebo-controlled, 4-period crossover study of the abuse potential of nabilone compared to delta-9-THC and marijuana cigarettes. Twenty-four (24) male regular marijuana smokers participated; placement of subjects into groups was based on frequency of marijuana usage as defined by the investigator: regular users (one to three marijuana cigarettes daily); intermittent users (one to three marijuana cigarettes weekly); and occasional users (one to three marijuana cigarettes monthly).

Subjects were administered the following treatments: nabilone (2 mg), nabilone placebo, a standardized marijuana cigarette (1 gm containing 2% delta-9-THC), delta-9-THC capsules (17.5 mg), and delta-9-THC placebo capsules. Each subject received one active drug and 2 placebos on any given test day. The treatments were counterbalanced so as to control for order effects.

Regular and intermittent marijuana smokers ranked the "highs" in the following preference order: marijuana cigarettes, delta-9-THC, nabilone. Occasional users found an equivalent degree of intoxication between all three active treatments. All users discriminated active treatments from placebo.

In an operant paradigm, subjects were asked to work for preferred drug or money. Regular users all chose marijuana cigarettes as the treatment of choice. All the intermittent users chose marijuana except one who chose delta-9-THC. Five (5) of the occasional users chose marijuana cigarettes and 3 did not express a preference for drug or money.

Conclusions: Although a case could be made for marijuana cigarettes being more reinforcing than delta-9-THC or nabilone, a far less persuasive argument could be made for the differences in peak "high" noted between delta-9-THC and nabilone. The observed differences are small and considerable overlap existed between delta-9-THC and nabilone scores. As single doses of both drugs were tested, the differences may reflect slight differences in potency rather than intrinsic activity. Thus, this study also fails to show meaningful differences in the subjective effects profiles of nabilone and delta-9-THC. Accordingly, no differences in abuse potential are observed.

H. Overall Summary of the Safety Profile for Nabilone

The data reveals that the use of nabilone (or other related cannabinoids) is associated with a series of adverse events predominantly involving the CNS. In their worst form (e.g., psychosis, organic hallucinosis), these events make nabilone a potentially difficult, even dangerous, drug to use. Nevertheless, given the seriousness of the condition in which nabilone is used, the reversible dysphoric symptoms associated with its use constitute a reasonably acceptable risk if the product is used under the conditions proposed and recommended in its labeling.

In addition to the risks imposed by nabilone under its recommended uses, the product is at risk for diversion and abuse. The abuse potential of nabilone is high; in fact, the agency considers it equivalent to delta-9-THC. There is considerable overlap between the therapeutic dose range and the abusable dose range. Moreover, severe adverse psychotropic effects (delirium, hallucinations, toxic psychosis) can occur with the recommended dosing schedule. It is for these reasons that nabilone is being recommended for use as a secondary agent for patients who are treatment failures with conventional antiemetics.

Nabilone is being recommended for Schedule II status under the Controlled Substances Act.

I. Biopharmaceutics

Due to the severity of the condition to be treated with nabilone, and the serious consequences that may result from continued nausea and vomiting in patients refractory to standard anti-emetics, the firm requested and was granted a deferral of bioavailability requirements for good cause, as described under 21 CFR 22(e).

The sponsor will be required to complete, within one year of the approval of this application, the appropriate bioavailability, bioequivalence, and dose proportionality studies.

VI. Pertinent Advisory Committee Minutes:

The issue of the abuse potential of nabilone was discussed at the Drug Abuse Advisory Committee on April 28-29, 1983. Additionally, the abuse potential of a related compound (delta-9-THC) was discussed at the Drug Abuse Advisory Committee approximately two years earlier.

1. Drug Abuse Advisory Committee: June 29, 1981

At this meeting, the committee decided that the compound delta-9-THC, if and when it may be approved for use as an antiemetic in cancer chemotherapy, should be scheduled as a Schedule II substance under the Controlled Substances Act.

2. Drug Abuse Advisory Committee: April 28-29, 1983

At this meeting, the committee decided that nabilone and delta-9-THC possessed nearly similar potentials for abuse. Additionally, the committee recommended that nabilone be controlled under the Controlled Substances Act as a Schedule III substance. (The agency had recommended to this committee that nabilone be controlled as a Schedule II substance, given the similarities in potential for abuse to delta-9-THC, and the previous recommendations for that compound.)

The agency has evaluated these recommendations by the committee and has concluded that the abuse potential for each of these substances is identical, and that control under the Controlled Substances Act is most appropriate under Schedule II.

VII. Post-Marketing Surveillance:

Bioavailability, bioequivalence, and dose proportionality studies will be required (See V. I.).

VIII. Approved Package Insert:

A copy of the final approved package insert is attached.

MED REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-677

DRUG: pulvules Cesamet (Nabilone)

SPONSOR: Lilly

DATE: 12/13/85

TITLE: Response to approvable letter.

- 1) limited safety update.
- 2) change in product to rotary evaporated product.
- 3) ADME studies
- 4) draft labeling

REVIEW: Safety update.

CONTENTS:

The present update includes safety data on an additional 18 patients from the clinical trial data. Safety data for 683 patients was provided in the initial submission (Feb. 16, 1982) and on an additional 295 patients in the Sept. 20, 1985 safety report. Also included are safety data from international clinical investigations. Also, included are safety data from the international marketing of Cesamet (U.K. since February 1982 and Canada since February 1983).

1) Domestic Clinical Trial Experience

Thirty four events in 18 patients treated under Protocol 29 (compassionate use as antiemetic) are reported.

Also reported are 23 post NDA adverse events-see previous post-NDA report in the Sept. 20, 1985 submission.

The adverse experiences reported in both these groups is similar to previous data with 2 exceptions. In the protocol group "eye disorder" is reported separately from vision disturbances and is not otherwise clarified. In post-NDA patients discontinued because of adverse events (pg. 006) a cerebrovascular accident is reported. The remainder of the adverse events in both categories are unremarkable.

2) International clinical investigation experience

Adverse events reported from these international studies as of Dec. 8, 1985 are listed in Table 5, pg. 013 and all drop-outs because of adverse events or death in table 6, pg. 016.

The information for rising dose adverse events in table 5 is as

One death from hemorrhage is reported. Forty-nine patients discontinued because of adverse events and 12 because of death. The deaths are attributed to disease progression. One patient had convulsions. The ADR's are in the same distribution as previously reported with increased appetite and hallucinations the most frequent. There is no reason to alter previous conclusions regarding adverse drug effects.

Post-marketing spontaneous adverse event experience

The most frequent events reported were hallucinations, somnolence, dizziness, confusion, dry mouth and euphoria were next events only are reported, no denominator, so that relation to the size of the dose, to symptoms cannot be evaluated.

This data does not permit a statistical analysis of adverse events but the results agree with previous reports.

CONCLUSION:

These reports of adverse events agree with previous data regarding the high incidence of adverse events as well as the general agreement in the type of events encountered. CNS events remain the most prominent. The reported deaths are most likely not drug related.

Peggy A. Hanson, M.D.

cc: Orig. NDA
HFN-120
HFN-340
HFN-120/RKatz
/PHanson
ft/pjd/12/23/85
DOC#0410k

*ALL - Akathisia a newly reported ADR +
Go into labeling*

N-18677-2

REVIEW AND EVALUATION OF CLINICAL DATA OF NDA 18-677
ORIGINAL SUBMISSION

Date on cover letter of submission: February 16, 1982

Date Received in HFD-120: March 8, 1982

Sponsor: Lilly Research Laboratories
Indianapolis, IN 46285

Name of Drug: Nabilone (Generic Name)
Cesamet (Trade Name)

Related IND: This IND was submitted in 1974 for clinical testing as an anti-anxiety agent. Later, in 1976 phase 2 antiemetic studies were begun. The anti-anxiety studies were discontinued for lack of efficacy.

Class of Drugs: A synthetic cannabinoid for oral administration.

Sole Indication for the NDA Submission: For the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

Material Submitted: 24 volumes of which the last 2 volumes contain microfiche of individual raw data on 325 patients in a variety of nabilone studies.

Efficacy of nabilone for the control of nausea and vomiting occurring during cancer chemotherapy treatment is presented in 2 pivotal studies comparing: (1) nabilone against prochlorperazine (Protocol 20), and (2) nabilone against a placebo (Protocol 28).

Both protocols were multicenter, double-blind, randomized with crossover through 2 cycles of cancer chemotherapy. Safety was observed for use of nabilone and prochlorperazine regardless of whether the individual study was completed. After completion of 2 cycles, if the patient made the request, nabilone was re-instituted on open label and any subsequent adverse reactions were included.

The first efficacy study (Protocol 20) was performed in 3 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against prochlorperazine.

Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg spansule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour spansule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scale. The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In addition, monitoring of vital signs and laboratory studies were performed at intervals. These additional observations were of no value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Results of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1:

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cisplatin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients' observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
<u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
<u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
<u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

Safety Evaluation of

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20.

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and

bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	27
Same	1
Prochlorperazine better	8
<u>Severity of Nausea</u>	
Nabilone better	21
Same	10
Prochlorperazine better	5
<u>Food Intake</u>	
Nabilone better	18
Same	11
Prochlorperazine better	7
<u>Patient Preference</u>	
Nabilone better	29
Same	1
Prochlorperazine better	6
<u>Physician's Evaluation of Efficacy</u>	
Nabilone better	26
Same	8
Prochlorperazine better	2

Safety Evaluation of

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients

(41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

Study #3:

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriamycin in combination with other chemotherapeutic agents was one common denominator.

Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75) patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed to complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

Nabilone

Prochlorperazine

	NABILONE	PROCHLORPERAZINE	
	<u>Better</u>	<u>Better</u>	<u>Same</u>
Frequency of vomiting	42	24	9
Severity of Nausea	35	13	27
Food Intake	31	14	30
Investigator's Global Evaluation	47	9	19
Patient Preference	55	15	5

Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

<u>Adverse Reaction</u>	<u>Most Common Adverse Reactions</u>	
	<u>Nabilone (111)</u>	<u>Prochlorperazine (103)</u>
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by body systems, the greatest number occurred in the nervous and psychiatric systems with nabilone. Most of these represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55

(62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control.

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nabilone was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1:

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of

chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytosan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
 <u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
 <u>Food Intake</u>	
Nabilone better	3
Same	7
Placebo better	1
 <u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
 <u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety: The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

Study #2:

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4

Severity of Nausea

Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1
<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation:

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

Conclusions on Safety:

A very large majority 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

Study #3:

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4:

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol

deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5:

This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 3 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19

Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	1
Same	3
Placebo better	32

Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

Adverse Reactions:

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both

nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6:

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	23
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2

Same	5
Placebo better	25

Efficacy Conclusions

This group of patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions -

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%) experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)
Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	9 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #621 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo:

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in

their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
Jones	11
Einhorn	33
Greco	5
Durant	8
Levitt	36
Gunnell	36
TOTAL	<u>129</u>

Efficacy results are combined in the following comparison in similar manner to the individual studies.

	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32
Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99(77%)	15(12%)	15(12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3

Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Epilogue

Two submissions were received since submission of NDA 18-677 on 2/17/82.

- 1) Date of submission 2/23/82. Received in Drug Abuse Staff 4/14/82. Included 2 F1639s on death's of patients. Both patients were in Protocol #28 (nabilone-placebo). Both had extensive carcinoma and died of their disease. Deaths were not drug related.
- 2) Date of submission 3/22/82 consisting of annual report. Reviewed by Drug Abuse Staff on 4/12/82. Report of 1 death attributed to lung carcinoma. This patient was in the placebo cycle and had not received nabilone.

Conclusions:

Nabilone is approvable for efficacy on the basis of clinical review. Nabilone was found to be superior to both prochlorperazine and placebo in the control of nausea and vomiting occurring in patients undergoing cancer chemotherapy.

Safety has to be evaluated on a risk vs benefit result. Adverse reactions

were much higher in the nabilone treated group cycles. The most common adverse reactions in descending order were drowsiness, vertigo, dry mouth, and alteration of taste. After completion of the study, a large majority (75%) of patients were able to continue nabilone for future chemotherapy cycles.

Before final approval is given for nabilone, the following recommendations are made:

1. Consultation with HFD-150, Division of Oncology and Radiopharmaceutical Drug Products in regard to:
 - a. Concurrence with appropriateness of the chemotherapy schedules with patients disease as selected by the sponsor. Do these patient's illnesses and treatment comprise the usual caseload of an oncologist?
 - b. Concurrence with oncologist's experience with prochlorperazine with dosage and times of administration.
 - c. Assistance with labeling of package insert.
2. Consultation with Drug Abuse Staff in regard to drug abuse potential. This will include scheduling the drug.
3. Confirmation of statistical analysis of study by the Division of Biometry.

Margaret A. Milliken

Margaret A. Milliken, M.D.
Medical Officer, HFD-120

cc:

Orig: NDA 18-677

HFD-120

HFD-180

HFD-120/FVoccl

HFD-120/MMilliken/EBarker

rd/mb/8/25/82/FT/8/31/82/DOC 3554B

Robert J. Barker

CESAMET - Lilly
NDA 18-677

V. Medical Summary Basis of Approval:

A. Introduction:

Nabilone "Cesamet" is a synthetic cannabinoid for oral use. It is supplied as 1.0 mg capsules. The sole indication for its use is severe nausea and vomiting occurring in patients receiving cancer chemotherapy.

B. Adequate and Well Controlled Studies:

The sponsor submitted 2 multicenter studies.

The first multicenter study (Protocol #20) was performed at 3 hospital centers, comparing Nabilone against a known antiemetic, namely, prochlorperazine. The results of these studies will be designated Protocol #20.

The second adequate and well controlled study (Protocol #28) was performed at 6 medical centers in which antiemetic results were compared with patients receiving placebo while undergoing cancer chemotherapy.

Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg spansule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour spansule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scale. The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In

addition, monitoring of vital signs and laboratory studies were performed at intervals. These additional observations were of no value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Results of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1:

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cisplatin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic

drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
 <u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
 <u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
 <u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

Safety Evaluation of Study (Investigator 003)

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients

with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20,

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	27
Same	1
Prochlorperazine better	8
<u>Severity of Nausea</u>	
Nabilone better	21
Same	10
Prochlorperazine better	5
<u>Food Intake</u>	
Nabilone better	18

Same	11
Prochlorperazine better	7
<u>Patient Preference</u>	
Nabilone better	29
Same	1
Prochlorperazine better	6
<u>Physician's Evaluation of Efficacy</u>	
Nabilone better	26
Same	8
Prochlorperazine better	2

Safety Evaluation of (Investigator 302)

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients (41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

Study #3: Protocol 20,

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriomycin in combination with other chemotherapeutic agents was one common demoninator.

Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75) patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed to complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

	<u>Nabilone</u>	<u>Prochlorperazine</u>	
	<u>Better</u>	<u>Better</u>	<u>Same</u>
Frequency of vomiting	42	24	9
Severity of Nausea	35	13	27
Food Intake	31	14	30
Investigator's Global Evaluation	47	9	19
Patient Preference	55	15	5

Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

<u>Adverse Reaction</u>	<u>Most Common Adverse Reactions</u>	
	<u>Nabilone (111)</u>	<u>Prochlorperazine (103)</u>
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by body systems, the greatest number occurred in the nervous and psychiatric systems with nabilone. Most of these

represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55 (62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nab. was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity

of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1:

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytosan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
 <u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
 <u>Food Intake</u>	
Nabilone better	3

Same	7
Placebo better	1
<u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
<u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of Investigator (001):

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety: - The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

Study #2: _____

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1
<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and

cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation:

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

Conclusions on Safety:

A very large majority 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

Study #3:

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one

dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4:

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5:

This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 3 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19
Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	1
Same	3
Placebo better	32

Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

Adverse Reactions: Study (005)

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6:

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	23
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2
Same	5
Placebo better	25

Efficacy Conclusions

This group of patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions - Study

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%) experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)

Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	9 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #621 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo:

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
	11
	33
	5
	8
	36
	36
TOTAL	129

Efficacy results are combined in the following comparison in similar manner to the individual studies.

	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32

Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99(77%)	15(12%)	15(12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3
Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

NDA 18677

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Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Margaret A. Milliken

Margaret A. Milliken, M.D.

mb/1/27/83
DOC #4883

Medical Officer Consultation on NDA 18-677

NDA: 18-677

Applicant: Eli Lilly and Company

7 1982

Name of Drug: Generic Nabilone
Trade Cesamet

Dose Form and Route: 1 mg pulvules for oral administration.

Proposed Indication: For control of nausea and vomiting due to cancer drugs.

Clinical Evaluation:

Efficacy is demonstrated in two pivotal studies of double blind, randomized prospective crossover design. One study compares nabilone with the standard antiemetic prochlorperazine and the other study compares nabilone with placebo. Nabilone toxicity is quite significant.

Comments and Recommendations:

1. The prochlorperazine dose is at the low end of the range generally used.
2. A complete response category (no nausea or vomiting) would be helpful. However, the parameters used are (in toto) adequate.
3. Cancer chemotherapy drugs may not all produce vomiting by the same mechanism. An antiemetic effective for one cancer drug may not be effective for all others. In addition some cancer drugs cause severe vomiting and others little if any. The approval of metoclopramide (Reglan) is restricted to nausea and vomiting due to cis platin. In the TrC NDA applicant showed results of TrC with each of several chemotherapy regimens.

It is probably not feasible to test each antiemetic with all existing anticancer drugs and certainly not with all combinations of these drugs in use. Applicant has studied nabilone with a reasonably representative spectrum of cancer drugs with emphasis on those causing the most severe nausea and vomiting. However, the results should be broken down into separate categories according to the cancer drug given with emphasis on those cancer drugs known to cause the most severe vomiting. The following categories are suggested: cis platin based regimens, non cis platin based regimens, DTIC based regimens without cis platin, adriamycin based regimens without cis platin or DTIC, Cytosin based regimens without adriamycin, DTIC or cis platin and any regimen occurring with sufficient frequency to make evaluation meaningful. We should not require nabilone to be

effective in each of these subcategories of the .05 level of significance, but one wants to see at least a favorable trend in all or most categories if labeling indicates efficacy for all cancer chemotherapy drugs.

4. Package Insert:

- (a) Cancer patients often have impaired liver function. There may be need for reduced dose in these patients as there is for THC. Both are excreted via the bile.
- (b) In the PRECAUTIONS, GENERAL section "tranquilizers and sedatives" should be added at the end of the first sentence.
- (c) The PATIENT INFORMATION section should indicate the patient should be accompanied by a responsible adult who can do any driving and remain with the patient for 24 hours after drug administration or until all drug side effects have subsided. This would be consistent with THC labeling.
- (d) Is there any indication of tolerance with nabilone?
- (e) The proposed schedule (first dose the night before) appears different than that used in the well controlled trials.

John R. Johnson M.D.
John R. Johnson, M.D.
11/22/82

cc: Orig, NDA 18-677
HFN-150
HFN-150/Div File
HFN-220
HFN-150/Johnson
HFN-150/Ripper/Behrens
F/T by P. Amoss/11/24/82
Wang #00038

W. Ripper
11/24/82

AUG 2 1983

Second Review and Evaluation of
Clinical Data of NDA 18-677

Data on Cover Letter of Submission: February 16, 1983

Data of Completion of Second Review: July 27, 1983

Medical Officer's First Review Completed: August 31, 1982 and approved by
Acting Group Leader, Dr. Eileen Barker

Medical Officer's Second Review: Refer to Memo of Division Director dated
July 5, 1983 (attachment)

Sponsor: Lilly Research Labs
Indianapolis, Indiana

Name of Drug: Nabilone (generic)
Cesamet (trade)

Related IND/NDAs: 3

This IND was submitted in 1974 for clinical testing as an anxiety agent. In 1976, phase II antiemetic studies were begun. The antianxiety studies were discontinued for lack of efficacy.

Class of Drugs: A synthetic cannabinoid for oral administration

Sole Indication for the NDA Submission: For the control of nausea and vomiting caused by chemotherapeutic agents in the treatment of cancer

Material Submitted: 24 volumes of which 2 volumes contain microfiche of raw individual data on 325 patients. In addition since submission on February 6, 1982, the sponsor has submitted follow-ups in 3 volumes which include experience with adverse reactions.

Review of Cesamet for Efficacy and Safety

Phase I, Protocol 1,

This was a single dose ranging study using 3 human male volunteer prisoners. Dosage range of nabilone varied from 0.1 mg to 5.0 mg. Conclusion of investigator was that nabilone in doses less than 3 mg produced no effect. Nabilone at 3 mg. produced euphoria, dry mouth. At dosage at 5 mg, subjects experienced postural hypotension, dry mouth, and euphoria.

Conclusion Phase I, Protocol 1: Continue testing limiting top dosage to 5 mg/per day.

Phase I, Protocol 2: Effects of multiple doses of nabilone in 3 human male volunteers

Dosage was 2 mg three times daily for 7 days

Each subject experienced nausea, dizziness, drowsiness and blurred vision

Postural hypotension was evident in each of the subjects

Protocol 7 - early phase II dose ranging study - Part I

Clinical Investigators -

Protocol 7, Part I is the first clinical study of dose ranging in 13 cancer patients who had experienced nausea and vomiting during chemotherapy and who were resistant to prochlorperazine. This was an open study with pregnancy being the only excluding factor.

Nabilone dosage was given three times daily ranging from 1 mg three times daily as compared with 2 mg three times daily. Nabilone was given 30 minutes before start of intravenous cancer chemotherapy.

Monitoring consisted of observation, BP every four hours, recording patient's statements and a complete battery of blood studies before and after drug usage.

Results were inconclusive. Most patients felt partial improvement under each dosage. None received complete relief. There were no serious adverse reactions; the recorded observations are quite similar to the phase I studies; namely drowsiness, dry mouth, and dizziness. Mild hypotension was observed in only 1 patient on the lower dose of nabilone (1 mg t.i.d.)

Conclusion: 13 patients who had received no relief from previous cycles of prochlorperazine experienced some improvement on 2 dosage ranges of nabilone.

Protocol 7, Part II (See Protocol #20, Study 2)

Protocol 9, Vol. 9 p.9: This was a late phase II study, testing nabilone at 1 mg or 2 mg with comparison with prochlorperazine at 5 mg and 10 mg. Purpose was to standardize a dosage schedule and protocols before starting phase III studies.

Investigator:

Ninety-eight (98) patients entered the study of which 83 patients completed two cross over cycles. Most of these patients (75) received cisplatin for testicular or ovarian cancer.

Final dosage form was determined at completion of the study using all 96 patients who were eligible to evaluate dosage level although only 83 were considered candidates for efficacy evaluation. The following doses were selected:

	Daily Dose	No. of Patients
Nabilone	less than 2.0 mg	10
	2 mg to 4 mg	35
	4 mg or more	51
		<u>96</u>

The discrepancy in total numbers is that some patients never finished the cross over or broke protocol for other reasons.

Dosage conclusion for future phase III studies

Nabilone - 2 mg every 12 hours

Prochlorperazine 10 mg every 12 hours

Efficacy value was based on (1) frequency of vomits, (2) severity of vomits, (3) and food intake using rating of: (1) None = 0, (2) Mild = 1, (3) moderate = 2 and (4) severe = 4.

Clinical comparison of efficacy observation:

Clinical comparison of efficacy observation:

Frequency of vomits	Number of patients
Nabilone better	62
Same	7
Prochlorperazine better	14
	<u>83</u>

Severity of Nausea

Nabilone better	52
Same	15
Prochlorperazine	14
	<u>81</u>

Food Intake

Nabilone better	40
Same	30
Prochlorperazine	11
	81

Safety Observations

The largest number of patients treated with nabilone experienced both Central Nervous System and Psychiatric Manifestation Drowsiness in 84 patients receiving nabilone as compared with 80 patients with prochlorperazine; vertigo in 72 nabilone patients compared with 36 patients on nabilone.

The next largest adverse experiences were a "high" feeling observed in 44 patients on nabilone although 7 patients receiving prochlorperazine reported a "high" feeling.

Ortho-static hypotension was observed in 3 patients on nabilone.

Conclusions: Protocol 9 was valuable in determining protocols in phase III studies. From this experience, the 2 pivotal studies were developed as a double-blind cross-over, comparing the efficacy and safety of nabilone to either prochlorperazine or placebo. Moreover, the dosages were determined as were the conduct and analysis of major testing.

Phase III studies are designed to observe the efficacy of Cesamet in control of nausea and vomiting to cancer chemotherapy when compared against compazine (Protocol #20) and against placebo. Review of these studies follow.

Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg capsule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour capsule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scales.

Rating scales were the following:

<u>Nausea</u>	<u>Food Intake</u>	<u>Global Impressions</u>
0 = none	0 = none	1 = very good
1 = mild	1 = less than usual	2 = good
2 = moderate	2 = usual amount	3 = fair
3 = severe	3 = more than usual	4 = poor
		5 = very poor

Regarding vomiting scales: The patient had to have at least 2 less vomiting episodes on Day 1. To achieve a rating of better, the number of vomiting spells had to be at least 50% less than the corresponding cross-over study.

The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In addition, monitoring of vital signs which included postural hypotension of lying and standing blood pressure and pulse rate at 2 hours after receiving medication and laboratory studies were performed at intervals. These laboratory studies consisted of hematology, urinalysis, SMA-12 to be done prior to use of each study drug. These additional observations were of little value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. No EKGs were routinely made. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Performance of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1:

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cisplatin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
<u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
<u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
<u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

Safety Evaluation of _____ (Investigator 003)

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed

crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20,

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who

entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	27
Same	1
Prochlorperazine better	8
<u>Severity of Nausea</u>	
Nabilone better	21
Same	10
Prochlorperazine better	5
<u>Food Intake</u>	
Nabilone better	18
Same	11
Prochlorperazine better	7
<u>Patient Preference</u>	
Nabilone better	29
Same	1
Prochlorperazine better	6
<u>Physician's Evaluation of Efficacy</u>	
Nabilone better	26
Same	8
Prochlorperazine better	2

Safety Evaluation of _____ (Investigator 302)

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients (41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

Study #3: Protocol 20,

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriamycin in combination with other chemotherapeutic agents was one common demoninator.

Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75) patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed to complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

	<u>Nabilone</u>	<u>Prochlorperazine</u>	
	<u>Better</u>	<u>Better</u>	<u>Same</u>
Frequency of vomiting	42	24	11
Severity of Nausea	35	13	27
Food Intake	31	14	30
Investigator's Global Evaluation	47	9	19
Patient Preference	55	15	5

Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

Adverse Reaction	Most Common Adverse Reactions	
	Nabilone (111)	Prochlorperazine (103)
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by body systems, the greatest number occurred in the nervous and psychiatric systems with nabilone. Most of these represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55 (62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nabilone was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1:

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytosan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
<u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
<u>Food Intake</u>	
Nabilone better	3
Same	7
Placebo better	1
<u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
<u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of Study - Investigator (001):

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety: - The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

Study #2:

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1

<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation:

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

Conclusions on Safety:

A very large majority, 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

Study #3:

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4:

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5:

This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence - evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 3 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19
Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	1
Same	3
Placebo better	32

Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

Adverse Reactions: (005)

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6:

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the

cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	13
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2
Same	5
Placebo better	25

Efficacy Conclusions

This group of patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions -

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%)

experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)
Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	0 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #621 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo):

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
	11
	33
	5
	8
	36
	36
TOTAL	129

Efficacy results are combined in the following comparison in similar manner to the individual studies.

	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32
Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99 (77%)	15 (12%)	15 (12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3
Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated

for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Comments on Consultations:

Statistics were reviewed by Dr. Nevius. I discussed his review with him on June 15, 1983. Protocols 7 and 9 were done as early as phase I and II to establish dosage and safety guidelines. Three of the 4 studies (protocols 9, 20 and 28) produced statistical evidence of efficacy.

Oncology consultation was reviewed on November 24, 1982 by Dr. Johnson in HFN-150, Division of Oncological and Radiopharmaceutical Drugs. I discussed with him on July 18, 1983 the variety of cancer chemotherapeutic regimens that had been treated with Cesamet. As in his memo, he felt that drugs such as Cesamet should be used in patients receiving drugs known to cause severe n and v such as cis-platin. Further, there appear to be sufficient patients that received cis-platin with Cesamet to limit the labeling at this moment for use with cis-platin only. "Reglan" (metaclopramide) still has limited use to cisplatin only. Dr. Johnson re-stated that the mechanism of nausea and vomiting may not be the same for the various carcinogenics.

Epilogue

Two submissions were received since submission of NDA 18-677 on 2/17/82.

- 1) Date of submission 2/23/82. Received in Drug Abuse Staff 4/14/82. Included 2 F1639s on death's of patients. Both patients were in Protocol #28 (nabilone-placebo). Both had extensive carcinoma and died of their disease. Deaths were not drug related.
- 2) Date of submission 3/22/82 consisting of annual report. Reviewed by Drug Abuse Staff on 4/12/82. Report of 1 death attributed to lung carcinoma. This patient was in the placebo cycle and had not received nabilone.

Conclusions and Recommendations:

In view of Dr. Leber's memo to me dated July 7, 1983, I pass on making recommendations to Dr. Leber.

Margaret A. Milliken
Margaret A. Milliken, M.D.
Medical Officer, HFN-120

N-18677-3

Attachment:

Memorandum to File
NDA 18-677
(Cesamet, nabilone)
July 5, 1983

Subject: NDA 18-677 review package submitted by Dr. _____ for supervisory review.

Attention: Dr. _____

The single most important review of an NDA, the review which is expected to integrate the views of each reviewing discipline into a cohesive whole, is the Medical Officer's Review. Your review of NDA 18-677, (i.e., an undated review of some 19 pages, and the 1 page addendum to it of June 27, 1983), not only fails to meet this goal, but fails to meet standards for a review focused only upon the clinical data submitted.

Consequently, your review and its associated documents (i.e., draft labeling, SBA, draft letter, etc.) are inadequate to support your recommendation that the product be approved.

The NDA review package suffers from the following defects:

1. The Medical Officer's Review describes only two so-called "pivotal" studies, Protocols 20 and 28. Other studies submitted to the NDA are not described. For example, Protocol 7 and Protocol 9, each described in the review by the statistical consultant, are not even mentioned in the Medical Officer's Review. Moreover, the Medical Officer's Review does not enumerate, in any place, the extent and type of data submitted by the sponsor. Official FDA BD Staff Manual Guide policy makes clear that an enumeration and review of all studies is required. This includes both clinical pharmacology (Phase I and Phase II) and safety data from any and all clinical studies including clinical studies to assess the product as an anxiolytic (i.e., the 1974 submission).
2. The studies that are the subject of the Medical Officer's review are described with inadequate detail.

a. The review fails to describe the protocol used in either of the two 'pivotai' multicenter studies in adequate detail. For example, it fails to state whether the cross-over design employed was counter-balanced. This design takes into account the order of treatment administration and is an essential feature of any adequate and well-controlled crossover study.

b. The review fails to describe the rating devices used in a manner that would allow anyone reading the review to understand how they were employed or what they measured.

c. The review of data is limited to conclusion about global efficacy for each of two treatment cycles. There is no review of the actual data on which these conclusions are based. For example, the observed difference in vomiting under the treatments compared is not presented in quantitative terms. Neither a severity of nausea, food intake and preference of patients.

3. The organization of the data elements reviewed and the plan of the review does not follow the suggestions of the consult review received from HFN-150. Dr. Johnson suggested specifically that several categories of anti-tumor chemotherapy be evaluated to determine whether or not Cesamet's alleged anti-nauseant activity was general or limited to specific types of chemotherapy (e.g., see 2nd paragraph, item 3, of the consult review, dated 11/22/82).
4. The two protocols reviewed by the medical officer (i.e., No. 20 and No. 28), are inconsistently and inadequately evaluated.

In Protocol 20, the items reviewed for efficacy in each of the three sub-studies are not the same. In Study No. 1, the outcome of four items is examined, while in Study No. 2, five outcome measures are examined. The results of Study No. 3 under protocol 20, are not enumerated at all.

Failure to enumerate the results of the last study make it difficult to interpret the accuracy of the composite data presented.

A similar problem affects protocol No. 28 and its description. Six rating categories are used to assess efficacy; however, in each of the six sub-studies, different items from this group of six efficacy variables are tabulated. Consequently, it is impossible to tell from the data representing the composite of the six studies which trials contributed which results.

5. There is a lack of internal consistency in the review concerning the outcome of events in each study. In particular, in Study No. 28, the number of individuals (i.e. 13) in which placebo was better than Cesamet,

as tabled by Dr. on page 17, is five fewer than the number obtained by adding together the number of individuals from the four individually tabled sub-studies in study No. 28 (2 studies were not individually tabled). Clearly, this is not logically possible and represents an error. There are other examples of this sort of failure to check tabled data. On page 7 of the Medical Officer's Review, the tabulated number of patients evaluated for patient preference is 75. Of these, 55 are said to have liked nabilone better than the comparison treatment. However, in the first segment of this study, 18 patients preferred nabilone, in the second, 29; thus, two studies contributing 47 subjects to this rating category.

For the Table to be correct, 8 subjects would have had to prefer nabilone in the study. However, the Bressler study only had 7 patients who were considered evaluable. On page 14 in describing the Levitt study, the text and table for the same item, patient preference, contradict one another. This lack of internal consistency raises concerns about the reliability and accuracy of the review.

5. The Medical Officer's Review fails to enumerate and evaluate basic data that bears on the safety of the product. There is no assessment of vital signs, blood pressure or laboratory data. Admittedly, one might expect great variation among the patients given their wide variety of cancers and treatments. Nevertheless, each patient's response under treatment can be compared with his own baseline rating and any differences observed can be compared among the treatments.
7. The Medical Officer's Review fails to assess the effect of dropouts on the study. While the biometric review did attempt an analysis, the Medical Officer's Review makes no comments about this issue. Obviously, the first period of a counter-balanced crossover design can be used as a parallel study. It is important to assess the outcome of all patients who received at least one treatment to see whether or not their response contradicts any conclusion regarding the efficacy of nabilone that is based solely upon subjects who completed the trial.
8. The omissions and errors in the Medical Officer's Review are carried over into the draft Summary Basis of Approval. Indeed, the medical sections of this document are little more than a direct restatement of the incomplete Medical Officer's Review.
9. The labeling review and the modification to the indications section suggested by the Medical Officer are not justified in the review. It is not evident what reason the medical officer has for restricting the Indication for nabilone use as an anti-nauseant to patients "who do not receive relief from the use of standard antiemetic drugs."

The labeling also fails to include any mention of the pharmacologist's view (given in the SBA) that the evaluation of the safety and efficacy of nabilone only allows for its short-term use in cancer patients. This caution is not given in the labeling.

Conclusion:

The evaluation package, especially the Medical Officer's Review, is not adequate to support the approval of this drug product. A conscientious and systematic effort must be made to (1) display the data fully, (2) make certain that the data is accurate, (3) ascertain the nature of the rating scales and the variables actually rated (i.e., actual counts of vomiting episodes and severity of nausea, rather than better and worse categorizations), (4) assess the outcome using all participants in the two pivotal studies (20 and 28) who had at least one full treatment cycle on any anti-nauseant, and (5) most important of all, carry out a full safety evaluation (i.e. vital signs, BP, laboratory) supported by full statistical review. The latter is especially important, as there is a suggestion that this drug product produces hypotension, and possibly tachycardia. We must examine the effects of nabilone on blood pressure, EKG, and standard laboratory tests. In short, a much more thorough and full analysis of the data of this application is essential before we consider it ready for supervisory review.

Recommendations:

- 1 - The Medical Officer is to undertake immediately to correct the deficiencies enumerated in this memorandum.
- 2 - The completed medical review should be considered as the Medical Officer's first priority, and must be completed by July 30, 1983.

cc:
NDA Orig.
HFN-120
Dr. Leber
Dr. Barker
HFN-120/PLeber/7/5/83
FT/dcm/7/5/83/ft/mb/7/5/83/ft/IScott/7/28/83
Doc. 6816B

Signed P. Leber (MAM)
7/5/83

REVIEW AND EVALUATION OF CLINICAL DATA
SAFETY REVIEW

NDA 18-677

Sponsor: Eli Lilly and Co.

Drug: Generic: Nabilone
Trade ; Cesamet

Chemical: (+)-Trans-3-(1,1-dimethylheptyl)6,6a,7,8,10,Hexahydro-1-hydroxy-6,6-dimethyl-9-H-dibenzo[b,d]pyran-9-one

Category: Cannabinoid

Indication: Control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

Route of Administration: 1 mg and 2 mg tablets for oral administration.

Submission Date: February 16, 1984

This submission consisted of 25 volumes and case reports submitted on microfiche. The original studies testing the drug for a variety of indications including metabolic studies, antianxiety, and glaucoma are included in the safety reviews. The major studies for antiemetic effect in cancer chemotherapy consists primarily of multicenter trials 20 and 28 and prochlorperazine controlled trials 7 and 9. These studies are also included in the safety review and are discussed first.

Background:

Nabilone is an orally absorbed synthetic cannabinoid with CNS effects similar to 9-tetrahydrocannabinol (9THC). It was originally hoped to have less toxicity and has been tested as an antianxiety agent. The present NDA would limit its use to the nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

The original formulation was poorly bioavailable and to overcome this difficulty a new process (ethanol dissolved drug mixed with polyvinylpyrrolidone (PVP)) was used to produce 3 formulations for which a comparative bioavailability study was performed. This was subsequently deemed inadequate (Hebb - Biofarm. Rev. 5/22/83) but it is of note that in the clinical studies to be reviewed different formulations were used.

Pharmacology:

1. Antiemetic Effects:

- (a) In cats BCNU produced vomiting in 50% of animals with a latency of 145 minutes (10-20 mg/kg) After pretreatment with Nabilone it failed to elicit vomiting in any of 14 trials.
- (b) In cats mechlorethamine elicited prompt vomiting with 15 minutes latency in all animals. Following Nabilone it produced vomiting 2 of 8 trials after latency of 209 minutes.
- (c) Nabilone did not block apomorphine emesis in the dog.

2. Effects on vomiting induced by cisplatin in pigeons: Nabilone was 80-160 times more potent than prochlorperazine (?species specific).

3. Nabilone effect on spontaneous motor activity and general behaviour was assessed in mouse, rat, cat, dog and rhesus monkey. The general effect across species was depression of motor activity and depression of normal behaviour suggesting that a sedative effect would be observed in humans.

Preliminary tests showed that Nabilone was active in analgesic tests but was not antagonized by Naloxone. In morphine-dependent monkeys undergoing withdrawal Nabilone suppressed retching and vomiting but not other signs of abstinence (mydriasis). Therefore it was considered non-opiate like.

Nabilone produced ptosis, dozing, mydriasis, ataxia and reduced responsiveness and was more potent than 9THC but in a 30 day test increasing tolerance to behavioural effects were noted. Cross-tolerance with 9THC but not with morphine was demonstrated.

In the dog static ataxia test Nabilone produced ataxia and body sway at 32 mg/kg. Two metabolites were tested and also produced ataxia the RRS metabolite more than the SSS metabolite. Brain concentrations of the SSS Carbinol can concentrate in the brain in dogs. This may account for the species specific high toxicity in dogs.

Human Studies:

Several studies were conducted in humans to elucidate pharmacology, pharmacokinetics and metabolism. Although few patients were involved in each study the side effect data were included in summary with data from other studies. They will be included in our summary.

SAFETY ANALYSISIntroduction:

Nabilone was originally thought to be less toxic than 9 THC and was introduced in humans for a number of indications including its use in glaucoma and as an anti-anxiety agent. The sponsor, however, decided because of toxicity to limit the indication for use of Nabilone to treatment of the emesis accompanying cancer.

A number of studies were begun which were interrupted during the study. However, safety data on all the patients who received Nabilone is included. Toxicity was striking in all studies and adverse experiences with a 5% or greater incidence is listed.

Individual studies are described below and the location of the data is indicated.

For all studies the modified Cornell Medical Index (Vol. 1.9, Appendix III, p.467) was used for scoring side effects in all patients.

A summary of adverse experiences with a 5% or greater incidence is listed on p.359.

**ADVERSE EXPERIENCES OCCURRING WITH A 5% OR GREATER INCIDENCE
DURING THE CROSSOVER STUDIES AND DURING OPEN-LABEL STUDIES
(Drug-Related and Unknown Drug Relationship)**

Adverse Experience	Total Pts. No. of Patients	436 Percent
Drowsiness	285	65.4
Vertigo	267	61.2
Salivary Secretion Disturbance (Dry Mouth)	125	28.7
High*	116	26.6
Ataxia	55	12.6
Depression	44	10.1
Concentration Decreased	42	9.6
Vision Disturbance	39	8.9
Headache	37	8.5
Sleep Disturbance	32	7.3
Euphoria	30	6.9
Asthenia	29	6.7
Depersonalization Syndrome	28	6.4
Hypotension, Orthostatic	23	5.3

*The term "high" is not precisely defined. In the crossover studies using prochlorperazine as a control drug (269 patients), the patients were asked on a daily questionnaire if they were "high". At the same time, in 2 of these

studies (Investigators 201 and 203) patients were asked if they were sad or "low". Without further clarification to the patients in the prochlorperazine-controlled studies, it is not possible to accurately assess the percent incidence of a marijuana-like high or euphoria. In the placebo-controlled studies (199 patients), these questions were not asked. The percent incidence of a high in these latter studies was 2.2, while the percent incidence of euphoria was 9.8.

The most important studies were multicenter protocol 20 (prochlorperazine controlled) and protocol 28 (placebo controlled). These protocols are analyzed first. The additional protocols 7 and 9 which were also prochlorperazine controlled are then reviewed. The safety data from these 4 studies has been summarized and the combined studies have been reviewed.

Following these studies the remainder of the small studies or incomplete studies are then reviewed for safety. Although individual studies were often small the description of side effects in these early studies is comprehensive.

In all these studies a Modified Cornell Medical Index (Vol. 1.9, Appendix III, p.467) was used for scoring side effects in all patients.

3 formulations of Nabilone have been used:

- I. One was prepared by a rotary evaporation procedure. Most of the clinical work was performed with this formulation.
- II. Another was prepared by a granulation procedure. Some of the work in the later stages utilized this formulation.
- III. A third was a formulation of Nabilone in starch. I and II utilized Nabilone and PVP co-precipitate. In III Nabilone alone was placed in a starch formulation. These 3 formulations were considered bioequivalent (see review).

Human studies to be reviewed first consist of the two pivotal multicenter studies:

1. Protocol 20 - Cesamet with prochlorperazine as active control. (Studies 7 and 9 are also prochlorperazine controlled and will be reviewed subsequently).
2. Protocol 28 - Placebo controlled.

Protocol 20:

Title: A Study of the Antiemetic Effectiveness of Nabilone.

This is a double-blind, randomized crossover study. Drugs were given in two consecutive cycles of cancer chemotherapy.

	<u>Cycle 1</u> Day	<u>Washout</u>	<u>Cycle 2</u> Day
Sequence Group I	1,2,3,4,5 Nabilone	3-6 weeks	1,2,3,4,5 prochlorperazine
Sequence Group II	prochlorperazine	3-6 weeks	Nabilone

The study drug was administered concomitantly with the chemotherapy which was administered over a period of 1 to 5 days. (See Protocol).

Young Study 301:

For the first study (Young) chemotherapy was administered for 1 to 2 days only. The test drug was generally extended to one day thereafter.

Of 55 patients who received Nabilone day 1, 40 or 73% received it on day 2. Of 52 patients who received prochlorperazine on day 1, 39 (75%) received the drug on day 2.

Most intense cancer chemotherapy generally was administered on day 1.

Drug doses were Nabilone (Cesamet) 2 mg bid and prochlorperazine 10 mg bid. Not all patients received the total calculated dose on each day.

FREQUENCY OF PATIENTS BY TOTAL DAILY DOSE

	<u>DAY</u>						
	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Nabilone							
2 mg	51	16	10	3	1	1	1
4 mg	1	39	30	0	0	0	0
Greater than 4 mg	-	-	-	-	-	-	-
TOTAL	52	55	40	3	1	1	1

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FREQUENCY OF PATIENTS BY TOTAL DAILY DOSE

	<u>DAY</u>						
	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Nabilone							
2 mg	51	16	10	3	1	1	1
4 mg	1	39	30	0	0	0	0
Greater than 4 mg	-	-	-	-	-	-	-
TOTAL	52	55	40	3	1	1	1

Prochlorperazine					
10 mg	48	14	8	1	1
20 mg	2	38	31	1	1
30 mg	-	-	-	-	-
Greater than 30 mg	-	-	-	-	-
TOTAL	50	52	39	2	2

Only patients in whom it was anticipated that the cancer chemotherapy would remain the same during the two consecutive cycles, and who had experienced nausea and vomiting during at least two previous cycles of chemotherapy were admitted to the study. A variety of diagnoses and cancer chemotherapy were permitted in the study. Generally multiple drugs were most common on day 1. The study results were reported separately for two groups, those who received Cisplatin with other combinations and those who received other combinations without Cisplatin. Patients were also divided by high ($> 100 \text{ mg/M}^2$) and low ($< 100 \text{ mg/M}^2$) of Cisplatin.

However, adverse experiences or side effects were not reported separately by either of these criteria. These are reported only related to the drug administered (Nabilone or prochlorperazine).

Safety evaluation was based on the following:

1. Vital Signs - Specifically the relationship of recumbent and standing blood pressures at baseline and 2 hours following each drug dose.
2. Patient daily report of adverse effects in questionnaire (e.g., Modified Cornell Medical Index (Vol. 1.9, Appendix III)). At the end of the study the investigator recorded an impression of the relationship of each adverse effect to the study drug.
3. Laboratory studies performed prior to the study between the cycles prior to cycle 2.

Statistical Evaluation of the adverse effects was limited to numbers of patients experiencing each effect and a summary of those adverse experiences with a 5% or greater incidence. No risk/benefit calculation was made. Adverse experiences were analyzed by the magnitude of the daily dose (less 2.0 mg Nabilone or $> 2.0 \text{ mg}$ Nabilone, $< 10 \text{ mg}$ prochlorperazine or $> 10 \text{ mg}$ prochlorperazine). Adverse experiences during open-label administration of Nabilone in those patients who elected to continue one drug were also reported although open-label administration was terminated.

67 patients entered the study, 43 males, 24 females ages 18-77. The most common chemotherapy was Cisplatin in combination with vincristine for lung, bladder and testicular cancer. 10 patients chose to continue open-label Nabilone.

The most common adverse experiences were drowsiness, vertigo, dry mouth and "high".

The adverse effects are reported on a total of 58 patients. These 58 patients presumably are those who received at least one dose of Nabilone on one cycle of the study.

The number of adverse experiences were apparently not related to dose for Nabilone but were dose related for prochlorperazine.

Study Drug	Average* Daily Dose	No. of Patients In Group	Drug Related	Patients Reporting At Least One Adverse Experience	
				Unknown	Drug Related Or Unknown
Nabilone	Less than 2.0 mg	14	9(64.3%)	5(35.7%)	13(92.9%)
	2.01-4.0 mg	41	22(53.7%)	12(29.3%)	31(75.6%)
	Unknown	3	2(66.7%)	1(33.3%)	3(100.0%)
Total		58	33	18	47
Prochl.	Less than 10 mg	13	2(15.4%)	3(23.1%)	5(38.5%)
	10.01-20 mg	40	9(22.5%)	16(40.0%)	22(55.0%)
	Total	53	11	19	27

Patient and investigator evaluations at the conclusion of the crossover study included patient overall preference between the two treatments and the investigator's global impressions, grading of severity of response by the following grading system and an assessment as to whether drug-related or unknown.

Adverse Experience:

Grading:

(1) None

(2) Did not significantly interfere with patients functioning.

(3) Significantly interfered with patient's functioning.

(4) Outweighed the therapeutic effect.

The latter would be some comment on risk/benefit ratio although not based on statistical data.

Dropouts:

I. Reasons for Early Termination.

28 patients were terminated early.

Of these, 3 were clearly drug related and occurred on Nabilone and two were due to adverse experiences of unknown cause.

1. Case 09 - Following one 2 mg dose of Nabilone experienced dysphoria, dizziness, nausea and decreased ability to concentrate.
2. Case 28 - Cycle II of crossover, single 2 mg dose. Experienced hallucinations, somnolence, dyspnea, dizziness, numbness, confusion and visual distortions.
3. Case 36 - Single 2 mg dose. Cycle I did not like the "high" experienced and discontinued no drug.

Two questionably drug related were:

1. Case 14 - One 2 mg dose of Nabilone followed by a discovered drop-in WBC and chemotherapy was postponed. Patient also had chills, weakness, restlessness and insomnia, dizziness and hypotension. Removed from study by the investigator.

Comment: This may well represent severe ADR to drug.

2. Case 52 - Prochlorperazine day prior to chemotherapy. Following the 10 mg dose on the second day he reported dizziness, "high" and loss of equilibrium. He did not return for initiation of chemotherapy.

Comment: It is clear that some patients anticipated a "high" and their discontinuation of the drug was related to this. Whether this also affected the blind is unknown but the prochlorperazine case (#52) makes it unlikely that patients were always sure of what constituted an appropriate "high" or a side effect.

3 patients dropped out for lack of efficacy on Nabilone and 3 on prochlorperazine.

II.

- a) 58 patients received at least one dose of Nabilone.
- b) 10 chose to continue Nabilone on an open label basis.
- c) Of the 67 randomized patients 58 received at least one dose of Nabilone and 53 received at least one dose of prochlorperazine and adverse experiences are analyzed in these patients.
- d) No correlation was made between high dose Cisplatin, low dose Cisplatin and no Cisplatin regarding ADR's. However, of the evaluable (32) patients the investigator's global impression of ADR's is as follows:

	<u>High Dose Cisplatin</u>	<u>Low Dose Cisplatin</u>	<u>None</u>	<u>Combined</u>	
				<u>C</u>	<u>NC</u>
Nabilone better	- 2	3	1	5	1
Same	- 8	2	3	10	3
Compazine better	- 3	3	7	6	7

- e) 33 of 58 patients (56.9%) who received Nabilone reported at least one drug related experience, 11 of 54 patients (20.8%) on compazine reported at least one ADR.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Drug Related and Unknown Drug Relationship)

<u>Body System</u>	NABILONE (Total Patients 58)		PROCHLORPERAZINE (Total Patients 53)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	4	6.9	2	3.8
Eye and Ear	2	3.4	3	5.7
Gastrointestinal	14	24.1	3	5.7
Metabolic and Endocrine	1	1.7	0	-
Miscellaneous	11	19.0	10	18.9
Nervous System	38	65.5	19	35.8
Psychiatric	17	29.3	6	11.3
Respiratory	1	1.7	0	-
Skin and Appendages	0	-	1	1.9

A COMPARISON OF ADVERSE EXPERIENCES WITH A 5% OR GREATER
INCIDENCE ON EITHER THE NABILONE OR PROCHLORPERAZINE CYCLE

(Drug Related and Unknown Drug Relationship)

<u>Adverse Experience</u>	NABILONE (58 Patients)		PROCHLORPERAZINE (53 Patients)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	23	39.7	14	26.4
Vertigo	23	39.7	7	13.2
Salivary Secretion Disturbances (Dry Mouth)	13	22.4	2	3.8
High (Euphoria)	11	19.0	2	3.8
Asthenia	5	8.6	2	3.8
Concentration Decrease	5	8.6	0	-
Excessive Appetite	5	8.6	0	-
Sedated	5	8.6	2	3.8
Sleep Disturbance	5	8.6	3	5.7
Headache	1	1.7	3	5.7
Hypotension	3	5.2	1	1.9

Table 3 gives the rank order of those ADR's occurring with a frequency of 5% or greater. It is clear that on all listings nervous system symptoms are most common and that ADR's were much more common with Nabilone. As in early studies single doses of 2 mg were accompanied by significant incidence of side effects.

In every category ADR's from Nabilone exceeded those from Compazine.

Conclusion

In this 2 day chemotherapy trial with one group of high-dose Cisplatin adverse reactions were most common in the central nervous system and were far more common with Nabilone than with control (compazine). The incidence of patients with at least one side effect was 56.9%. Single 2 mg doses were associated with side effects and led to 3 - possibly 4 dropouts.

- (1) "BP was obtained erect and recumbent in each hospitalized patient approximately 2 hours after each dose of medication and also as outpatients if they remained in the treatment setting."

There were many patients on which BP was not obtained and few in whom a full complement was obtained.

Data was available in 24 patients and "missing" in 16 to a total of 40 patients. It is not clear how this is selected from the 58 patients evaluated for safety.

Where available Nabilone showed a decrease in systolic pressure 14 patients vs. an increase in 9. A decrease occurred in 5 and an increase in 18 on prochlorperazine. The diastolic was affected in the same direction but with less striking difference (increase) in the Compazine treated group for both erect and recumbent pressures (Vol. 1.10, pg. 285-286).

No data regarding changes in laboratory data is given; however, review of patient values showed no significant deviations.

Protocol 20

Investigator: 302

This was the identical protocol.

49 patients (39 males and 10 females) enrolled in the crossover. 32 of the patients had testicular cancer which was usually treated with 5 days of Cisplatin with bleomycin and vinblastine generally administered concomitantly on day 1. Adverse reactions by incidence and by body system (Table 4) were similar to those found by investigator 301 despite the fact Cisplatin and other chemotherapy was only given for 2 days in 301 rather than 5 as in 302.

Incidence is based on 43 total patients (vs. 36 evaluable patients).

No distinction was made by the investigator between drug related and non-drug related experiences: both are listed together.

79.1% of Nabilone treated patients vs. 35.7% of Compazine treated patients reported at least one adverse experience.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Unknown Drug Relationship)

<u>Body System</u>	NABILONE (Total Patients 43)		PROCHLORPERAZINE (Total Patients 42)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	3	7.0	0	7.1
Eye and Ear	3	7.0	3	7.1
Gastrointestinal	5	11.6	3	7.1
Genito-Urinary	1	2.3	1	2.4
Miscellaneous	13	30.2	8	19.0
Musculoskeletal	2	4.7	6	14.3
Nervous System	30	69.8	4	9.5
Psychiatric	19	44.2	2	4.8
Respiratory	3	7.0	2	4.8

Early Terminations (Dropouts)

45 -Only one patient clearly terminated as a result of adverse experience. She received 2 days of Nabilone treatment and complained of dizziness, dry mouth, blurred vision, depression urgency, anxiety, ataxia and photophobia.

Two other patients on Nabilone experienced adverse effects which led to failure to complete Cycle 2.

#46 received Nabilone 8 mg for 5 days. He complained of a "high" and dizziness. He experienced a focal seizure. He was on Lithium 300 mg tid and had a low serum sodium but this is not given in the laboratory data all of which are normal. Hemogram is not given. (Vol. 1.21, pg. 6?).

#54 received 4 mg Nabilone and complained of drowsiness, fatigue, a floating feeling, myalgia and joint pain. Failed to return for Cycle II.

Two patients on prochlorperazine also failed to return. The complaints were not clear. #47 had sore throat, chest pain, headache, backache and neck ache.

Drug Dose

65% of patients who received Nabilone on day 1 continued drug through day 5 vs. 67% for prochlorperazine. Only eight patients received more than 4 mg on any given day.

In the statistical analysis on every comparison the difference between adverse effects on Nabilone vs. chlorpromazine was either not significant or showed significantly more adverse effects on Nabilone. Despite this 29 of 36 evaluable patients (81%) favored Nabilone.

Vital Signs and Labs

Blood pressure analysis for both recumbent and erect pressures and systolic and diastolic showed either no significance or a larger decrease or smaller increase on Nabilone. Examination of the records showed that a larger portion of the patients had BP recordings complete than under previous investigator. No abnormalities of laboratory data appeared significant on inspection. Elevated SGOT was observed in patients who began the study with elevated SGOT.

Comment:

The incidence of adverse reactions on Nabilone is again high (80%) and always higher than prochlorperazine. No serious reaction is recorded.

Protocol 20

Investigator: 306

This was a small study, 10 patients (4 males and 6 females) were entered. 3 patients terminated the study and 7 were considered evaluable. All patients received at least one dose of Nabilone.

Dropouts:

- #1 received a single 2 mg dose of Nabilone. She experienced hallucinations, nausea, vomiting, nosebleed and also blurred vision lasting 2 days. She continued to feel "high" and dizzy on day 2.
- #9 received 2 X 2 mg doses. She discontinued both drugs for lack of efficacy but later stated Nabilone was better than prochlorperazine.

Blood pressure changes were so seldom recorded they could not be analyzed. No significant laboratory abnormalities were experienced.

80% of patients on Nabilone reported at least one adverse effect and 6 patients had at least 9 occurrences of ADR's related to the nervous system.

Comment:

This short study shows no findings regarding side effects at variance with the previous two studies.

Summary of Protocol 20:

I. Patients receiving at least one dose Nabilone.

(301)	58
(302)	43
r (306)	10
	<u>111</u>

N.B. One patient on open label only was later included in analysis.

II. Early Termination (ADR):

	<u>Nabilone</u>	<u>Prochlorperazine</u>	<u>Unknown</u>
301	3	None	2
302	3	2	None
306	1	0	0

Early Termination (Lack of Efficacy):

301	3 -(4)	3 (4)
302	0	0
306	1	1

III. # of Patients reporting at least one drug-related adverse experience:

	<u>Nabilone</u>	<u>Prochlorperazine</u>
301	known 33/58 (56.9%) +unknown 47/58 (81%)	<u>11/53 (20.8%)</u> 27/53 (50.9%)
302	known +unknown 34/43 (79.1%)	15/42 (35.7%)
306	known 3/10 (30.0%) +unknown 7/10	None 3/10 (30%)
	<u>K + UK 88/111 = 79%</u>	<u>45/103 = 43.6%</u>

IV. All studies gave highest priorities to nervous system.

Complications: CNS	<u>Nabilone</u>	<u>24.3%</u>
CNS	66.7%	CNS 24.3%
Psychiatric	34.2%	9.7%

<u>Adverse Experience</u>	<u>NABILONE</u> (Total Patients 111)		<u>PROCHLORPERAZINE</u> (Total Patients 103)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	7	6.3	2	1.9
Eye and Ear	6	5.4	7	6.8
Gastrointestinal	21	18.9	6	5.8
Genito-Urinary	1	0.9	2	1.9
Metabolic and Endocrine	1	0.9	0	-
Miscellaneous	25	22.5	20	19.4
Musculoskeletal	2	1.8	6	5.8
Nervous System	74	66.7	25	24.3
Psychiatric	38	34.2	10	9.7
Respiratory	5	4.5	2	1.9
Skin and Appendages	0	-	1	1.0

N.B. Hypotension, hypotension orthostatic, and syncope were rare (Nabilone 8/8 and prochlorperazine 2/2) considering that the general trend was to a drop in BP with Nabilone and a rise in BP with prochlorperazine. No instance was reported as severe. Only 75/126 had blood pressure follow-up.

Protocol 28

Title: A placebo-controlled study of the antiemetic effectiveness and safety of Nabilone in patients with nausea and vomiting caused by cancer chemotherapy.

Study Plan:

This was a multicenter double-blind, randomized, crossover study comparing Nabilone with placebo given during two consecutive cycles of cancer chemotherapy involving 6 investigators.

Study Design:

<u>Cycle 1</u>	<u>Washo. t</u>	<u>Cycle 2</u>	
<u>Day</u>	<u>3-6 Weeks</u>	<u>Day</u>	
<u>1,2,3,4,5</u>		<u>1,2,3,4,5</u>	
Group 1 Nabilone		Placebo	Open Label
Group 2 Placebo		Nabilone	nabilone

Only patients expected to remain on the same regime of cancer chemotherapy during the two consecutive cycles of the crossover study were included. Patients on high dose Cis-platinum (over 100 mg/M²/day) were excluded (cf. Protocol 20). Patient assignment was stratified to insure balanced distribution of patients who have not had prior cancer chemotherapy and those who have had prior chemotherapy. Drug dose was 2 mg bid.

Study 00:

24 patients (8 males and 16 females) ages 20 to 78 were enrolled. 11 were considered evaluable (less than 50%). 22 patients received at least one dose of Nabilone. 11 patients discontinued the crossover study early.

II. Diagnosis:

- 8 = lymphoma
- 4 = breast cancer
- 4 = ovarian cancer
- 8 = other

III. Cisplatin:

6 received cisplatin in one of the cycles
18 did not receive cisplatin.

IV. Dropouts:

4 due to adverse experience - Nabilone - 104, 109, 118, 126

Nabilone related adverse experiences:

1. dizzy, drowsy, orthostatic hypotension
2. dizziness, nausea and vomiting
3. drowsiness, dizziness and ataxia
4. drowsiness, dizziness

2 due to adverse experience on placebo -#113, 115

1 due to lack of efficacy on Nabilone - 120

2 due to lack of efficacy on placebo -#116, 121

3 patients (open label) discontinued for intoxicated feeling, orthostatic hypotension, drowsiness and dizziness.

V. ADR's:

18 of 22 patients (82%) on Nabilone had at least one adverse experience vs. 4 of 21 patients (19%) on placebo.

The usual predominance of CNS symptoms was observed. Most were "mild or moderate" in severity. Hypotension was present in 3 patients.

Age, sex and dose were not related to incidence of adverse reactions. 2 patients (one open label) discontinued for orthostatic hypotension.

Investigators global impressions clearly favored placebo over Nabilone (Nabilone 1.64 vs. placebo 0.18 - (Mean Values)

Only one episode of hypotension is described during the study proper and this was considered severe (3) but blood pressure recordings are incomplete in crossover and therefore cannot be meaningfully compared.

Laboratory abnormalities were generally present at baseline and could not be attributed to drug.

Comment: This is a small study in which many factors do not reach significance especially with more than 50% of patients excluded.

Adverse reactions were in the 80% range with Nabilone and much higher than placebo.

Orthostatic hypotension occurred only with Nabilone.

Protocol 28Investigator 002

Study is still in progress. This is a report of the findings to date (1982).

42 patients (23 males and 19 females) between the ages of 16 and 63 were enrolled. 42 were evaluated for safety (at least one dose of drug).

33 patients were considered evaluable and the investigator's global impression of adverse experiences are available for these and indicate that placebo was better than Nabilone in 32 of 33 patients (p .001).

There was a striking difference in the vomit frequency for Cycle I vs. Cycle II.

I. Dropouts:

4 patients discontinued the crossover study early due to adverse experiences vs. none on placebo. 4 discontinued due to lack of efficacy on placebo.

Adverse Experiences:

- #204 - 2 doses of 2 mg Nabilone gave sleepiness, lightheadedness, dysphoria and decreased coordination before chemotherapy started.
- #205 - One 2 mg dose; severe vertigo, nervousness and dry mouth.
- #224 - 2 doses of 2 mg Nabilone; drowsiness, dizziness, dry mouth, headache and dysphoria.
- #237 - 4 days of Nabilone. Patient experienced drowsiness, lightheadedness, orthostatic hypotension.

II. Drug:

9 out of 21 patients received cisplatin.

40 patients took drug on day 1 but only 19 on day 2 and less thereafter.
14 took 5 days of Rx.

III. 41 of 42 patients (98%) experienced at least one adverse effect.

4 of 35 patients (11%) who received placebo experienced at least one adverse effect.

CNS symptoms predominated as in other studies.

4 patients experienced orthostatic hypotension - severe.

Sex, age and dose were not related to incidence of adverse experiences.

Blood pressure fell in all measurements to a statistically significant degree. A significant proportion of patients had more than one BP recorded.

2 patients on open label dropped out due to adverse experiences.

Laboratory data were not significantly abnormal.

Comment:

Again a high percent of adverse effects (98%) was noted with Nabilone.

BP decreases were frequent and 4 cases of orthostatic hypotension were observed.

No like threatening adverse effects occurred.

Patients preferred Nabilone.

Investigator 003

14 patients (14 males, 10 females) between 37 and 67 years of age were enrolled. 4 patients had ovarian cancer, 4 breast and 4 lung and other. The most frequent therapy was one day of cisplatin, adriamycin, cytoxan and hexamethylmedamine.

11 of the 14 patients received at least one dose of drug and were evaluated for safety.

6 continued an open label study and ADR's are included.

9/11 patients (82%) experienced at least one adverse experience.

I. Dropouts:

One patient dropped out for Nabilone ADR following a 2 mg dose: she experienced hallucinations, was sleepy and incoherent.

One patient discontinued placebo for lack of efficacy.

Investigators global analysis of ADR's showed significant excess in Nabilone over placebo.

Hypotension was not reported but almost no patients had follow-up blood pressures.

Comment: A small study but no significant differences from those of the other investigators was noted.

Investigator 004

16 patients (7 males and 9 females) between 26 and 80 years were enrolled. 8 patients were considered evaluable. 5 patients had breast cancer, 4 lung and 2 lymphoma. All 16 patients received at least one dose of Nabilone and all reported at least one adverse experience. No adverse experiences were reported on placebo. Nervous system and psychiatric systems showed the predominant symptoms. No hypotension is reported.

I. Dropouts:

4 patients terminated early due to drug related symptoms; one patient due to lack of efficacy on placebo.

#405 - One dose of Nabilone followed by a dose of Tigan resulted in continued vomiting prior to chemotherapy. Drug was discontinued.

#412 - 2 mg dose: weakness, dry mouth, dizziness, insomnia and "strange feelings" - "stoned" of 2-3 days duration.

#415 - 2 mg dose: dizziness, moderate vomiting and somnolence for 1 day prior to therapy.

#416 - Completed a 1 day cycle 1 on Nabilone but refused crossover due to drowsiness, dry mouth, nausea and "high."

Median daily score for investigator's global impressions of adverse experiences was 1.38 vs. 0.00.

In general, laboratory values when abnormal were abnormal at baseline.

No evaluation of BP is given, there is no report of hypotension. A small proportion of patients had follow-up blood pressures.

Comment: A small study but the 100% incidence of adverse reactions is typical of Nabilone.

Investigator: 005 Lewitt: (Vol. 1-13, p.12)

This study is still in progress.

58 patients (25 males and 33 females) age 17-79 were enrolled. 36% had lung cancer, 19% ovarian cancer and 10% breast cancer.

23 out of the 53 patients received Cisplatin as part of their chemotherapy. 51 patients received at least one dose of Nabilone.

The majority of patients received between 2 and 4 mg daily and ADR's were not related to drug dose (or age or sex).

II. Dropouts:

20 patients discontinued the study early.

5 discontinued due to drug related adverse experiences.

1 patient discontinued due to lack of efficacy of placebo and 1 for lack of efficacy of Nabilone.

Drug-Related, Nabilone:

#504 - One day Rx on Cycle II. Dizziness, dry mouth, nausea, decreased coordination and anxiety.

#516 One 2 mg dose: dizziness, sleepiness, anxiety and strange unusual feelings.

#517 - One 2 mg dose: severe dizziness and feeling weird -- lasted 1 day.

#566 - One 2 mg dose: shortness of breath, irregular pulse, dizziness and tightness of the chest.

#578 - One 2 mg dose of drug: drunk feeling and dizziness.

#563 - Was noted as related to lack of efficacy of Nabilone - patient refused Cycle II; however, in Cycle I he had refused to continue Nabilone because of felt "weird" on arising; dizzy, drowsy and "high."

#570 - Appears similar. He had drug-related fear, "weird" dizzy feeling and sleepiness during Cycle I. Refused Cycle II because he did not want "to be a guinea pig any more."

I. Results:

47 of 51 patients (92%) who received Nabilone had at least one adverse experience; 7 of 46 patients (15%) who received placebo reported at least one adverse experience. The principle adverse reactions were CNS or psychiatric. No hypotension was related in this study. It is of importance that in this study alone only one of the 58 patients enrolled is not included in the analysis -- all the others had sufficient BP recordings to evaluate changes.

This was borne out by inspection of the patient records. There were significant decreases on Nabilone. Recumbent systolic pressure: 41 decreases vs. 5 increases; placebo 16 decreases vs. 17 increases. Diastolic BP 18 decreases vs. 6 increases. Placebo 6 vs. 9 (.022 vs. .500). Standing blood pressure was even more impressive systolic. Nabilone 41 decreases vs. 2 increases (p .001) vs. 16 to 17 (p .500) for placebo and 14 to 6 (p .116) for Nabilone vs. 4 to 9 for placebo (.226) for placebo. Diastolic: 14 decreases to 6 (p .116) for Nabilone vs. 4 to 9 for placebo (.226).

This bears out the prior experiences where less complete records were available. As in other studies global impressions of adverse effects were strongly in favor of placebo (p .001).

Comment:

This is a very well carried out study; certainly the BP recordings are much more complete than in any of the other studies. Yet the results do not differ significantly from the others. This study of blood pressure could be considered pivotal.

Investigator 00:

45 patients (20 males and 25 females) in and outpatients between the ages of 29 and 78 were enrolled. 31% had breast cancer, 22% lung cancer and 9% ovarian cancer.

36 patients were evaluable. 10/45 patients received Cisplatin.

41 patients received at least one dose of Nabilone.

I. Dropouts:

4 patients terminated early due to adverse experiences on Nabilone.
3 patients on placebo terminated early due to lack of efficacy.

- #609 - Completed Cycle I (Nabilone) refused Cycle II because of severe dysphonia, dizziness, and decreased coordination.
- #625 - One 2 mg dose of Nabilone; severe lightheadedness, dysphonia and dullness.
- #639 - Day of Cycle I only - (?4 mg) severe drowsiness, dysphonia and dizziness.
- #704 - Completed Cycle I, refused Cycle II because of severe drowsiness, dry mouth, moderate lightheadedness, confusion and euphoria

II. Drug:

Only 1 patient took 5 days of Nabilone. 40 took at least one day of Rx.

Results:

32 of 41 patients (78%) who received Nabilone reported at least one adverse experience as against 2/41 patients who received placebo. The usual predominance of CNS symptoms and psychiatric symptoms was observed; vertigo, drowsiness, dry mouth and euphoria were most common. One episode of hypotension was noted.

They report no statistically significant decrease in BP with Nabilone over placebo, but the records have few follow-up blood pressures. Age, sex and dose had no effect on the incidence of adverse effects. Laboratory abnormalities were not significant. Global estimate of adverse reactions favored placebo over Nabilone (p .001).

Comment:

This is an unfinished study.

Blood pressures were not recorded in a number of instances or no follow-up blood pressure was recorded; one episode of hypotension occurred.

Findings did not differ from the other studies.

Summary: Protocol 28

A total of 199 patients (87 males and 112 females) were studied by 6 clinical investigations in which a double-blind crossover study compared the antiemetic effects of Nabilone to placebo. The patients were in the ages of 17 and 80 years. Ninety-eight patients were studied in the Treatment Group 1 and 101 in Treatment Group 2. Of these 199 patients, 129 (55 males and 74 females) were considered evaluable. Fifty-seven of evaluable patients were in the Treatment Group 1 and 72 were in the Treatment Group 2. More patients under the Treatment Group 1 were found to be unevaluable (41 of 98 patients) compared to the patients in the Treatment Group 2 (29 of 101 patients). The reason was that 16 patients terminated the study early because of adverse experiences while receiving Nabilone.

Fifty-two patients (26%) had breast cancer, 38 (19%) lung cancer, 23 (12%) ovarian cancer, 23 (12%) testicular cancer, and 23 (12%) lymphoma including Hodgkin's disease. The remaining 40 patients (19%) had many other types of cancers with the patient frequency of 4 or less for each cancer.

The most common cancer chemotherapy regimens consisted of Adriamycin and cyclophosphamide in various combinations with one or two other agents, or Cisplatin and Adriamycin in various combinations with one or few other agents. However, a break down of the cancer chemotherapy agents were made into two major groups with respect to Cisplatin and the frequency of both evaluable and unevaluable patients in each group was presented in Table 1. Of 109 evaluable patients, 84 received combinations of chemotherapy regimen with Cisplatin.

CANCER CHEMOTHERAPY BY EVALUABILITY AND SEQUENCE GROUP

Chemotherapy	Evaluable Treatment			Unevaluable Treatment		
	Group 1	Group 2	Total	Group 1	Group 2	Total
	Cisplatin + Other Combinations	19	26	45	15	8
Other Combinations Without Cisplatin	38	46	84	26	21	47
TOTAL	57	72	129	41	29	70

The total daily dose of Nabilone taken by the patients were analyzed and the results were shown in Table 2. The most frequent dose was 4 mg a day on the first day of chemotherapy. Of 167 patients who received Nabilone on Day 1, 20 patients (12%) continued to take Nabilone through Day 5.

FREQUENCY OF PATIENTS BY TOTAL DAILY DOSE
(Composite of All Six Investigators)

Total Daily Dose	Treatment Day								
	0	1	2	3	4	5	6	7	8
2 mg	183	22	6	2	2	3	-	-	-
4 mg	0	145	25	21	19	17	-	1	1
TOTAL	183	167	31	23	21	20	0	1	1

Adverse experiences were examined in 183 (of 199) patients who received at least one dose of Nabilone, and in 165 patients who received at least one dose of placebo.

168 patients (87.4%) on Nabilone and 18 of 165 patients on placebo (10.9%) reported at least one adverse experience - related to drug or unknown was not distinguished.

The most frequent symptoms on Nabilone were vertigo, dizziness and dry mouth. Ataxia and depersonalization were common. Drowsiness and vertigo were the most frequent adverse effects complained of on placebo.

The comparison of investigator's global impression of adverse effects was equally striking: means were 1.33 for Nabilone vs. 0.06 for placebo.

Among patients who chose to continue on open label study 53/55 reported adverse symptoms.

ADVERSE EXPERIENCES OCCURRING WITH A 5% OR GREATER
INCIDENCE DURING THE CROSSOVER STUDIES
AND DURING OPEN-LABEL STUDIES

(Drug-Related and Unknown Drug Relationship)

<u>Adverse Experience</u>	<u>Total Patients: 183</u>	
	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	110	60.1
Vertigo	109	59.6
Salivary Secretion Disturbance (Dry Mouth)	66	36.1
Ataxia	22	12.0
Depersonalization Syndrome	22	12.0
Sleep Disturbance	20	10.9
Dysphoria	19	10.4
Euphoria	18	9.8
Headache	17	9.3
Nausea	13	7.1
Disorientation	11	6.0
Concentration Decreased	10	5.5

SUMMARY OF REASONS TERMINATED

<u>Reason</u>	<u>No. of Patients</u>
Nabilone-Related Adverse Experiences	22
Placebo-Related Adverse Experiences	2
Adverse Experiences - Unknown or no Drug Relationship	3
Lack of Efficacy - Placebo	12
Lack of Efficacy - Nabilone	2
Lost to Followup	5
Patient Decision	6
Chemotherapy Changed	7
Progressive Cancer	2
Death (Cancer)	5
Complicating Conditions	1
TOTAL EARLY TERMINATIONS	<u>67</u>

Total Signs and Laboratory Data:

The records of blood pressure recordings are grossly deficient. Analysis of blood pressure was performed on 127 of a total of 199 patients. However, most studies did not have consistent, repeated measurements during both cycles of the study, and often only 2 blood pressures, one a baseline study are recorded.

The exception to this is Study 005. In this study all but one patient had frequent blood pressure recordings. The results clearly show a significant fall in both systolic and diastolic and erect and recumbent blood pressures on Nabilone. This study involving 58 patients could stand as a pivotal study of blood pressure. The changes confirm the analysis of the whole study which reported significant decreases in blood pressure (.02) with Nabilone.

Orthostatic hypotension was reported in 7 patients (3.8%). These are probably relatively severe reactions.

Adverse experiences were not analyzed for severity. Inspection of patient records show that a number were rated 3 or severe. An analysis of the severity of reactions could be prepared by the sponsor from data available.

Most important and in keeping with the development of tolerance with Nabilone is the fact that the majority of dropouts for adverse reaction occurred in patients who had only a single 2 mg dose.

It may be important to use rising doses and warn of adverse experiences to the patients if this were recommended as a back up drug for cancer chemotherapy nausea and vomiting.

Protocol #7

Title: Nabilone vs. Prochlorperazine in the Treatment of Nausea and Vomiting in Cancer Patients Undergoing Chemotherapy.

This was a double-blind, randomized crossover trial comparing the antiemetic effectiveness of Nabilone with that of Compazine (prochlorperazine) in patients with severe nausea and vomiting associated with anticancer chemotherapy.

The crossover was similar to the other controlled studies. The cycles is a course of chemotherapy usually administered over a 1-5 day period. The patient received either Nabilone or prochlorperazine in the first cycle and was crossed over to the other drug in the second cycle usually 3-6 weeks apart. The first dose of drug was administered on the evening prior to the first day of chemotherapy. Dose varied from 1 to 6 mg per day.

Efficacy and side effects were determined by a diary kept during the treatment period rating a) nausea and vomiting, b) euphoria, dry mouth, drowsiness, tachycardia and postural hypotension, time or distance distortion and inability to perform tasks requiring time coordination.

Subjects were interviewed daily. 43 patients age 17 to 70 years, 18 males and 25 females were enrolled. Fourteen patients were excluded due to protocol violations. 30 patients completed both cycles. 6 patients received cisplatin plus other chemotherapy. 17 received adriamycin plus other chemotherapies. The most frequent treatment was bleomycin, nitrogen mustard, procarbazine and vincristine. Most multiple chemotherapy occurred on days 1 or 2. All 43 patients received Nabilone but only 37 patients received Compazine.

Results:

1. Dropouts: 5 (?8) patients terminated early due to Nabilone related side effects and 2 due to prochlorperazine.

#10 -discontinued drug after second 2 mg dose due to orthostatic hypotension with syncope.

#23 -following one 2 mg dose patient complained of decreased appetite, decreased concentration and coordination, dizziness, drowsiness and dry mouth and refused to continue.

#48 -patient is scored as discontinuing due to both Nabilone and prochlorperazine. Cycle I was Nabilone and she experienced severe headache, pruritus and decreased appetite following 10 mg of prochlorperazine in Cycle II and discontinued the study. No description of Nabilone symptoms is given.

#43 -a single 2 mg dose of Nabilone was reported to have produced hallucinations, disorientation and toxic psychosis.

#50 -after one 2 mg dose of Nabilone (Cycle II) experienced decreased appetite, vision disturbance, decreased coordination, dizziness, drowsiness, dry mouth, euphoria, headache, hypotension, excess perspiration, weakness, nausea and vomiting prior to anti-cancer chemotherapy and discontinued drug.

#16 -discontinued after a full 6 day course of 6 mg of Nabilone due to side effects, mild to moderate drowsiness, visual disturbance, confusion, constipation, dizziness, dry mouth, euphoria, decreased urinary output and headache.

#28 -complained of nausea, dizziness, dry mouth and a "high" after the first 2 mg dose of Nabilone and refused to continue.

#29 -on a daily 6 mg dose complained of decreased appetite, vision disturbance, decreased coordination, depression, dizziness and dry mouth and refused to continue study.

#45 -reported nausea and vomiting prior to chemotherapy on 10 mg of prochlorperazine.

Drowsiness, dizziness and dry mouth were the most frequent complications. All of the 43 patients who received Nabilone (100%) and 35/37 patients who received prochlorperazine reported at least one adverse experience.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Drug Related and Unknown Drug Relationship)

<u>Body System</u>	<u>NABILONE</u> (Total Patients 43)		<u>PROCHLORPERAZINE</u> (Total Patients 37)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	15	34.9	3	8.1
Eye and Ear	24	55.8	8	21.6
Gastrointestinal	38	88.4	24	64.9
Genito-Urinary	6	14.0	4	10.8
Miscellaneous	20	46.5	17	45.9
Nervous System	43	100.0	27	73.0
Psychiatric	26	60.5	7	18.9
Skin and Appendages	3	7.0	1	2.7

Changes in blood pressure were significant only on recumbent systolic blood pressure. 10 patients had a greater decrease while on Nabilone while 2 had a greater decrease on prochlorperazine. Most patients had more than one B.P. recorded.

Comment:

This study of 48 patients is significant for safety data and confirms the high incidence of adverse effects on Nabilone. Syncope is reported from one case of orthostatic hypotension and the incidence of orthostatic hypotension was 18.6% vs. 0 for prochlorperazine.

This confirms data from other studies.

Protocol #9:

This was a double-blind, randomized crossover study evaluating the effectiveness and safety of Nabilone compared with prochlorperazine in the treatment of nausea and vomiting in cancer patients receiving chemotherapy.

The study plan included two cycles of chemotherapy 2-4 weeks apart with 1-5 days of chemotherapy at the beginning of each cycle with the first dose of study drug given 30 minutes prior to chemotherapy.

Dose: Nabilone was administered as a 1 mg capsule q 6h. p.r.n. and prochlorperazine as 5 mg capsule q 6h. p.r.n. The protocol was later amended so that the first dose was given on the evening before the first day of chemotherapy.

98 patients (83 males and 15 females) between the ages of 15 and 74. Two additional patients (101 and 102) were admitted directly to open label Nabilone and were evaluated for safety only. 52 of 96 patients (54.2%) continued Nabilone on an open label basis. One patient was entered twice (#12 and 67) and was evaluated for safety both times.

Results:**1. Dropouts:**

5 patients discontinued Nabilone because of adverse experiences. None discontinued prochlorperazine as a result of adverse experiences.

#11- Following 4 mg of Nabilone the patient experienced a high, moderate drowsiness, dizziness, depression, and reported feeling more anxious. She chose not to continue the drug. She reported having had a similar reaction on tylenol.

#14- Following 2 X 2 mg doses she complained of dizziness, nausea, bizarre dreams, strong and rapid heart beat and discontinued the drug.

#15- Took 3 days of drug (14 mg) and complained of a high, dizziness, severe drowsiness, dry mouth and difficult speech. She did not continue.

#44- After 2 mg of Nabilone in cycle II reported moderate drowsiness, depression and a high. He did not like how it made him feel and discontinued the drug.

No clear-cut 5th patient who discontinued because of Nabilone is reported.

II. 83 of 98 patients were considered evaluable.

76 of the patients had testicular cancer.

86 patients received Cisplatin with other combinations. Multiple drugs were usually given the first 2 days.

68/94 patients who received drug on day 1 (72%) received drug through day 5. The most frequent daily dose of Nabilone was 4 gm.

III. 96 patients received at least one dose of Nabilone.

90/96 patients (93.8%) reported at least one adverse experience.

74/92 patients taking prochlorperazine reported at least one adverse experience.

Adverse experiences were most frequently nervous or psychiatric as in previous studies. Drowsiness, vertigo, and a "high" were the most common reactions on Nabilone. 3 patients experienced orthostatic hypotension and one had syncope.

A significantly greater proportion of decreases of blood pressure were observed on Nabilone - (recumbent diastolic p 0-043), standing systolic (p .001) and standing diastolic (p .004). Most patients had more than one BP recorded in each cycle.

No laboratory abnormalities were considered significant by the investigator.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Drug Related and Unknown Relationship)

Body System	Nabilone (96 Patients)		Prochlorperazine (92 Patients)	
	No. of Patients	Percent	No. of Patients	Percent
Cardiovascular	5	5.2	2	2.2
Eye and Ear	2	2.1		
Gastrointestinal	3	3.1	1	1.1
Miscellaneous	25	26.0	27	29.3
Nervous System	88	91.7	69	75.0
Psychiatric	49	51.0	11	12.0

Comment: This is a relatively small protocol but all findings confirm those reported in other studies. Initial doses of Nabilone of 1 mg were not associated with dropout; one assumes that 2 mg was adopted as the dosage form because adverse reactions on the lower dose were less significant.

Summary of adverse reactions in prochlorperazine controlled studies (Protocols 7, 9, and 20).

	(#7)		(#9)		(#20)	
	N	P	N	P	N	P
Patients	43	37	96	92	111	103
ADR	43(100%)	35(95%)	90(96%)	74(80.4%)	88(79%)	45(43.6%)

Dropouts due to ADR's Protocols:

Summary #7, 9, and 20: (Total 18)

2 mg - 9
4 mg - 3
4 mg - 5

Summary dropouts due to ADR's Protocol 28;

2 mg - 16
4 mg - 3
4 mg - 9 ?+2

Total dropouts due to ADR's:

2 mg - 3
4 mg - 2
4 mg - 3

Totals:

2 mg - 38
4 mg - 8
4 mg - 15

Thus more than 3/4 of the patients who dropped out for Nabilone side effects had a dose of less than 4 mg; and most patients stopped the drug after a single 2 mg dose.

Analysis of Dropouts:

I. Study 7, 9, 20 and 28.

General:

Because the incidence of adverse effects is virtually 100% and because the patients receiving multiple chemotherapy for cancer were so sick the adverse effects were generally related without an attempt to distinguish those cases already drug-related and those that were not. A standard form -- the Modified Index Appendix III) was used throughout as a daily questionnaire to report adverse effects. The investigator was asked, where possible, to give an impression of the relationship of each adverse effect to drug. Most were listed together whether known or unknown.

Laboratory data were given in detail with high and low values indicated.

In Protocol 28 the abnormal data are listed separately in sections C-4 and C-5. If a low WBC was found the patient number and all WBC's were given.

In perusing the laboratory data some are unexplained and remained high throughout a number of determinations but generally, a) they were high at baseline, and b) the high values were not seriously elevated.

In each protocol the investigator was asked to evaluate the laboratory data and no serious reactions are described or attributed to the drug.

Vital signs and blood pressures were recorded but inconsistently. In statistical analysis the decreases of BP on Nabilone were significant. In only one study were BP's faithfully recorded (005). This study in which 58/59 patients had recorded BP's showed a decrease on Nabilone and this could stand as a significant study by itself.

Despite the tendency to low blood pressure only one patient was dropped out for syncope or orthostatic hypotension.

It is of interest that the majority of dropouts had received only a single 2 mg dose of Nabilone. In one study starting at 1 mg doses no comparable severe reactions are recorded. It suggests along with the evidence for rapidly developing tolerance, starting early with a low dose might be a reasonable strategy for using this drug.

II. Summary of patients with at least one adverse reaction:

(7) 43/43 or 100%	Prochlorperazine	35/37
(9) 90/96		74/92 (or) 154/232 (or) 66%
(20) 88/111		45/103
(28) 168/183 vs.	Placebo	18/165

TOTAL - 389 of 433 patients (or) 89%

I. Dose Ranging Studies:

Protocol 1 -

3 subjects, inmates of _____ received Nabilone as a co-precipitate with PVP in single oral doses of 0.1 to 5 mg. Doses were separated by at least 5 days in all three subjects, and the studies were single-blind with a placebo control. Side effects were elicited by a modified Cornell Medical Index. BP recordings were prior to drug and at varying intervals thereafter.

Results: The effects were dose related. At doses less than 3 mg there were no significant findings. At doses above 3 mg all subjects had dry mouth and euphoria. After 5 mg all subjects complained of dizziness on assuming the upright position, postural hypotension and slight tachycardia was documented.

It is interesting that subject D.M. described described a "high" on placebo on at least two occasions.

Protocol 1 - Amendment 1, 2, and 3:

Amendment 1 was to allow determination of plasma levels with a single dose of drug. Method developed for this is described in the appendix.

Amendment 2 was to enroll 6 additional subjects to obtain plasma level data.

Amendment 3 was to admit 1-2 additional subjects for plasma level.

Results: 9 additional male volunteers were used. All received a single 2 mg dose of Nabilone. All were administered a modified Index.

Results: 2/9 had no adverse experience
6/9 had dizziness or lightheadedness
7/9 drowsiness
4/9 euphoria
4/9 dry mouth
2/9 elation
2/9 headache
1/9 a different taste
1/9 had documented postural hypotension

Comment: This suggests that although inconsequential, side effects are experienced at doses less than 3 mg.

Protocol 2:

Effects of multiple doses of Compound 10951Y (Nabilone) in human male volunteers.

3 subjects given: (1) 1 mg bid X 7 days X 1 subject
(2) 2 mg bid X 7 days X 3 subjects
(3) 5 mg a single dose on day 7 X 3 subjects

- (1) The first patient showed mild symptoms on day 2 which disappeared.
- (2) On 2 mg bid all developed symptoms on day 2 and later were tolerant.
- (3) On a single added 5 mg dose after 7 days treatment minimal increases Index developed.
- (4) One week later challenge with 5 mg produced more marked effect.
- (5) Discontinuing drug was not accompanied by signs of abstinence.
- (6) A single subject received 50 uC. of ^{14}C labelled drug (without PVP) only 76% was recovered in feces and 4% in urine. This analysis was borne out by examination of the data. The blood pressure changes were inconsequential.

Amendment 1:

Nabilone 1 mg tid was given for 14 days to 6 normal volunteers. No placebo control was used.

Results: Standing BP was reduced (in 38 subjects) for the first few days and dry mouth and euphoria were common complaints. Tolerance was noted. By day 14 no untoward effects were noted. No withdrawal effects were noted.

Comment: Plasma concentrations and rates of decay following chronic administration (1 mg tid X 14 days) were similar to those following single doses. There is no evidence of drug accumulation. Safety, dry taste, headache were common and subsided with continued administration.

Protocol 7 -

Objective: To evaluate the effectiveness and safety of Nabilone in the treatment of nausea and vomiting in patients receiving cancer chemotherapy. Part I dose ranging (Part II compared to prochlorperazine).

13 patients who had experienced severe nausea and vomiting associated with parenteral cancer chemotherapy and who had been resistant to treatment with prochlorperazine were randomized to receive either 1 mg tid or 2 mg tid of Nabilone beginning 30 minutes prior to chemotherapy.

Efficacy: Therapeutic response was rated as none, partial or complete by the investigator.

Safety: Toxicity was rated as mild, moderate or severe.

Results:

Efficacy: <u>1 mg</u> none	- 1	<u>2 mg</u> none	- 0
partial	- 5	partial	- 5
partial-complete	- 1	partial-complete	- 1
complete	- 0	complete	- 0

Toxicity: Dizziness, decreased coordination, drowsiness and dry mouth were most common (approx.50%). 3 patients had severe reactions at each dose. No labs were abnormal.

It is stated that the investigators noted a feeling of dissociation which tended to persist 2-3 days after the Nabilone was discontinued.

Comment: Dose made no apparent difference in either effect or toxicity. Most all patients experienced some side effects - none serious.

II. Metabolism:

Protocol 3 -

Clinical Pharmacology Intravenous Study.

8 male patients received a single IV dose of either 0.25 mg, 0.5 mg or 1 mg to evaluate pharmacokinetics, metabolism and safety. (6 X 0.5 - 1 X 0.25 - 1 X 1.0). This was also a dose-finding study and the 1 mg dose was followed by marked side effects and the 2 mg dose was never given.

Results: 67% in feces and 20% in urine (7 metabolites in urine). After a single IV dose of ¹⁴C-Nabilone 0.5 mg mean plasma half-life was 20.6 hours. Estimated half-life of parent compared was 1.7 hours.

Side Effects: The one subject receiving a 1 mg dose was in acute distress describing a feeling of "emptiness, euphoria, restlessness, numbness, drowsiness and epigastric distress. This subsided promptly but there was a decrease in sensorium lasting 24-36 hours. One patient experienced postural hypotension. Six experienced dizziness, tachycardia, drowsiness and headache fatigue and euphoria. Only one patient had no side effects.

Comment: There is a limitation on IV dosage of this drug and most patients have drug-related side effects.

Protocol 5:

The disposition and metabolism of compound 109514 (Nabilone) in normal volunteers.

Study Oral: ^{14}C Nabilone was administered in a single oral dose of 2 mg (50 ^{14}C Nabilone) in PVP coprecipitate formulation to 2 subjects. Also a third subject received the starch formulation.

Results: 60% was eliminated in feces. The starch formulation had low plasma concentrations and more than 9% was excreted in feces unchanged.

Side Effects: Postural hypotension, dizziness, headache and general malaise was reported in the 2 subjects receiving PVP formulation.

Comment: The difference in the formulations is highlighted and the high incidence of side effects with low doses.

III. Bioavailability:

Protocol 30 -

Bioavailability study of Nabilone containing capsules using deuterated Nabilone oral suspension as an in vivo internal reference standard.

Study: Each of 4 males received a single dose of each of 4 formulations of Nabilone; (1) rotary evaporated 2 mg, (2) granulation 2 mg, (3) crystalline 2 mg in starch, and (4) oral suspension 2 mg.

Each was given together with 1 mg deuterated Nabilone oral suspension.

1 and 2 were bioequivalent, 3 was not, nor to the standard suspension. (See review Hepp - Protocol 30 unacceptable 2/17/82).

Adverse Reactions: All four subjects had side effects, 4/4 dry mouth and dizziness, 3/4 drowsiness and bitter taste, 2/4 weakness, increased appetite and "high".

Comment: Final word on the comparison of studies with different formulations will be needed. The ubiquitous presence of side effects is underlined.

Protocol 31 - Investigator:

Objective: To compare the abuse liability of Nabilone to delta-9-tetrahydrocannabinol (THC).

Design: 6 normal, healthy male volunteers who were experienced marihuana smokers capable of recognizing a "high" were assigned 5 regimes in a 5-way crossover study (placebo vs oral Nabilone vs IV Nabilone vs oral THC vs IV THC).

Results: IV THC appeared to be the most preferred of 5 regimes. Nabilone did not appear to produce the same degree of euphoria.

Four psychometric and psychomotor tests were recorded: (1) the wobble-board (balance-seeking movements), (2) attentive motor performance, (3) delayed auditory feedback system, and (4) mirror drawing test to test antianxiety effects.

Adverse experiences are tabulated for each subject but not combined. Drowsiness, decreased salivation and high were common. The effects were not qualitatively different than those to THC.

Comment: The similarity of adverse effects of Nabilone to those of THC are noted.

Protocol 33 -

Comparative assessment of reinforcing properties of Nabilone and marihuana.

Results in abstract only showed marihuana users chase marihuana. No adverse effects reported.

Protocol 35 -

Dose-Proportionality Study.

This was a four-way crossover study in which four subjects (volunteers) were assigned to four study treatments (1.5 mg Nabilone Suspension, 1 mg Nabilone-PVP, 2 mg Nabilone-PVP, 3 mg Nabilone-PVO) in a random order.

Adverse Experiences: All 4 subjects experienced dry mouth, drowsiness, dizziness. One experienced a high, one was sleepy and one had difficulty sleeping.

Comment: These are similar to other accounts of adverse reactions. All subjects (100%) experienced symptoms.

IX. Antianxiety Studies:

Safety data only - studies 6, 8, 10, 12, 14, 121, 221 with Nabilone in several different doses and diazepam or placebo as control.

This protocol was originally to apply to volunteer subjects age 18 through 48 years who were in good health and not on any treatment for anxiety; they were recruited on the basis of having high levels of state and trait anxiety as described on the basis of Hamilton Anxiety Score, Hopkins Symptom Checklist, Self-Rating Symptom Scale and a Raskin-Covi Rating of 8.

This study enrolled 157 subjects, 50 females and 107 males. In September 1978 it was decided to discontinue the study of Nabilone as an antianxiety agent because of hallucinations and altered mental state in patients who participated in antianxiety and antiemetic studies. Therefore the report gives safety data only and the data were combined from the following investigators.

Type	Controls	Investigator	Study No.	No. of Subjects	Nabilone* Dose (mg)	Frequency
Crossover						
Single-Blind	Placebo		8	9	0.5-4.0	Q-WKx9**
Double-Blind	Placebo		10	12	1.0-2.5	BID
Parallel						
Dose Ranging	None		12	5	1.0-4.0	BID
Double-Blind	Placebo		12	20	1.0	TID
Double-Blind	Placebo		121	8	1.0	TID
	+Diazepam*					
Double-Blind	Placebo		14	45	1.0	TID
	+Diazepam*					
Double-Blind	Placebo		6	49	2.0	1 dose
	+Diazepam*					
Double-Blind	Placebo		221	9	1.0	TID
	+Diazepam*					

* Diazepam dose was 5 mg per dose with a frequency matching the corresponding Nabilone schedule.

** Doses were given once-a-week for 9 weeks.

Of the patients enrolled 70 received Nabilone. The 5 continuous dose trials (10, 12, 121; 14, 221) were to last 12-28 days.

Summary: There were no life threatening events. The most frequent reported adverse experiences were dry mouth and drowsiness. No laboratory abnormalities were reported.

Six patients were considered dropouts due to adverse drug experiences. None of the diazepam control patients discontinued for drug.

#10 - This patient had previous drug addictions and alcoholism. After receiving Nabilone 1-2.5 mg for 5 days he developed all acute toxic encephalopathy thought to be secondary to unprescribed drug. He recovered.

#14 - This patient was on 1 mg TID X 3 days. He reported dizziness, headache, dry mouth, nausea and blurred vision and discontinued drug.

#6 - This patient received 1 mg TID for 8 days. She had initial orthostatic hypotension which was not considered related to drug. She had severe headache and nausea considered related to drug and discontinued medication.

#7 - This patient received 1 mg TID and discontinued drug after 2 weeks. She experienced nausea, loss of memory, confusion, a "high", speech defect, weakness, lightheadedness and missing her step. This was considered drug related.

#8 - This patient received 1 mg TID. She took drug for 12 days. She reported feeling moderately high with an increase in anxiety.

Safety Data on 70 Nabilone Patients:

Adverse experiences were not reported by decreasing incidence but dry mouth (21%), drowsiness (15.7%) were the most common symptoms. "High" is listed under CNS symptoms and was reported in 2.9% of patients.

It is noteworthy that in this study a separation was made between adverse experiences thought to be drug related (Table 1) and those not thought drug related. This distribution was not made on other studies and for comparison the results should be combined, e.g., dry mouth 21.4% + 8.6%, dizziness 4.3% + 2.9%.

Comment: The adverse effects reported on these studies are similar to those in other studies although most patients received only 1 mg/dose. The dropouts did not occur at the beginning of the study but after many days of drug administration.

Cesamet in Treatment of Glaucoma :

This study too was discontinued.

17 patients were enrolled and received drug.

5% of the patients reported 78.9% of the adverse effects.

This was a single dose (2 mg/mb) study. 5 patients received multiple doses.

5 serious adverse effects are reported. All but one had their adverse reactions after a single dose. In all a significant blood pressure drop occurred, e.g., to 70/40, 60/40, 60/40, 100/40, and one with "orthostatic hypotension". One patient after a single 1 mg dose was nauseous and fainted.

It is noteworthy that these patients were older than the patients in other studies (all but 2 were > 58 years). The symptoms experienced (excluding hypotension which is not recorded other than in the specific patient descriptions) were nausea, lightheadedness, drowsiness, dry mouth, faintness, giggling and vomiting. 12/17 patients reported minimal or no adverse experiences.

Comment: Most striking in this study is the frequency of hypotension following a single dose in older patients.

Study in "Emergency Use":

60 patients received Nabilone on an "emergency basis" for treatment of nausea and vomiting while receiving chemotherapy.

The drug was administered on an open label basis 2 mg BID the initial dose the night before chemotherapy.

The adverse reactions reported were: dizziness (15.3%), drowsiness (14.6%), dry mouth (6.7%). The others were said to be less than 5% incidence.

Overall Summary: These reports add nothing substantial to the safety reports in completed studies except the possible high incidence of hypotension in older patients with glaucoma.

Summary:

Convincing rationale for amelioration of nausea and vomiting in cancer chemotherapy have been adduced. When in extremis, as many of the patients are, considerations or risk/benefit may be altered from expectations in treatment of less disturbing conditions. Hence one might be prepared to accept a quantity or quality of side effects which might otherwise be considered intolerable. The consideration of using cannabinoids for adjunctive therapy is thus justified. The discussion of safety is undertaken in that light.

An overall review of the toxicity or side effects of Nabilone must take into consideration several factors which are general observations of treatment with Nabilone.

The first is that for practical purposes 100% of patients experience side effects with all doses of Nabilone.

This is most apparent in small Phase I and Phase II studies and in normal volunteers. These effects are generally what would be expected in a cannabinoid and must be evaluated in that light and with a view toward the degree of disability from nausea and vomiting. In the larger controlled studies the incidence of various side effects is tabulated and generally does not reach 100% but they are of the same nature as those reported in early studies; they were expected by the investigators and perhaps by the patients and these tabulations, therefore probably do not reflect accurately the incidence or perhaps even severity of side effects. Patient expectation may have a great deal to do with reporting of side effects; the lack of a "blind" when many patients recognize the drug as compared to active or placebo control may also affect these reports.

Of more practical immediate concern is the relationship of timing and dose to the side effects. In a drug in which for practical purposes there is a 100% incidence of side effects it is important to consider carefully those patients who dropped out of the study because of drug-related effects. The fact that the majority of dropouts occurred after a single 2 mg dose or two 2 mg doses (4 mg) is significant. In the 4 carefully controlled studies 38 patients dropped out after a single 2 mg dose, 8 after 4 mg and only 15 patients who dropped out received more than 4 mg suggesting that side effects severe enough to cause dropout generally occur with the first doses. This is not related to chemotherapy because these doses were administered prior to chemotherapy. It is interesting that in studies where a 1 mg dose was used initially less side effects are reported so that the size of the initial dose may well be important. The rapid development of tolerance is likewise well illustrated in Protocol 2 where rising doses were used in volunteers and a single 5 mg dose was well-tolerated after 7 days of treatment but could not be tolerated when reintroduced after washout. It may well be important that a factor to determine whether the risk/benefit of this drug is adequately to permit its use in severe nausea and vomiting is the size of the initial dose and its time relationship to onset of chemotherapy.

Another general concern is the development of hypotension. Despite the uniform experience of BP decreases (systolic and diastolic, erect and recumbent) the incidence of orthostatic hypotension is the lowest (5.3%) of the side effects reported and in other summaries of 5% or greater incidence disappears altogether. Also only one dropout for hypotension occurred - protocol #7, patient #10 but this required treatment. The record from the study by the only study in which the blood pressure recordings were complete confirmed the general reports. Thus, hypotension is of concern to the physician using this drug but is not by itself a contraindication to use of the drug but an issue for warning.

Conclusions:

The safety data on Nabilone show a high incidence of side effects, virtually 100%. Patients who dropped out generally did so after one or two 2 mg doses. Studies of blood pressure show a drop in pressure with Nabilone. The overall incidence of orthostatic hypotension is low but overall incidence less than 5% was not reported and individual instances of hypotension were not uncommon. Some studies are incomplete and a follow-up of years 1982-1984 should be requested with an update of the safety data.

Recommendations:

- (1) Tables of incidence of side effects should be reedited to show incidences of less than 1%.
- (2) Safety data should be updated and included in the above incidence tables.
- (3) The high incidence of dropouts after a single dose of drug should be emphasized and a study performed to elucidate whether slowly increasing doses were better tolerated but still antiemetic.

Cesamet Labeling:

Adverse Reactions:

- (1) A statement that for practical purposes 100% of patients can be expected to experience some adverse reaction with the drug. The most common A.R. are related to the nervous system or psychiatric. Drowsiness, vertigo and dry mouth are the most common. Orthostatic hypotension is a general finding and may result in syncope. This effect may be more prominent in the elderly.
- (2) The incidence of adverse effects should include all reactions including those with an incidence of 1% or less.
- (3) No change in listing by body symptom.
- (4) Data from protocol 28 and 20, 7 and 9 should, as suggested be submitted separately but a summary combining these studies for incidence should also be done.

Dosage and Administration:

- (1) There is evidence that tolerance to the adverse reactions to Cesamet is readily developed. It is suggested that where intolerance of the side effects of Cesamet might be expected to interfere with effective use of the drug dosage can be started with 1 mg 1-2 days prior to administration of chemotherapy slowly increasing to the expected 2 mg dose to be given before the oncolytic agent.



Peggy A. Hanson, M.D. (HFN-120)

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Review and Evaluation of the Clinical Data of
NDA 18-677

Applicant: Eli Lilly & Co.
Indianapolis, IN

1. General Information

a. Name of drug:

- (1) Generic - nabilone
- (2) Trade - CESAMET
- (3) Chemical - (+)-trans-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one

b. Category: Cannabinoid

c. Proposed indication: The sponsor is proposing that "Cesamet is indicated for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer."

d. Nabilone will be available in 1 mg (blue and white) and 2 mg (blue and green) pulvules for oral administration.

e. [Marinol, delta-9-THC; Levonantradol (investigational agent)]

2. Manufacturing Controls

I discussed the dosage forms of nabilone with Mr. Zinsitz, the reviewing chemist. He commented that the original formulation was poorly bioavailable and that the sponsor decided to manufacture the dosage form by a different process. Briefly, the initial dosage form contained 2 mg nabilone dispersed in starch in a capsule. The bioavailability was poor, as judged by 76% recovery in feces. Peak plasma concentration was observed to be 1 ng/ml at 30 minutes post-administration. To overcome the poor water solubility which resulted in the bioavailability problem, nabilone was dissolved in ethanol and mixed with polyvinyl pyrolidone (PVP), a water soluble polymer. Following evaporation of the ethanol, the dispersed nabilone: PVP co-precipitated in a 1:9 ratio. It was hypothesized that following ingestion, the G.I. contents would dissolve the PVP, thus liberating nabilone for absorption.

The nabilone: PVP co-precipitate was formulated using two manufacturing procedures, a rotary evaporation method and a granulation method. A comparative bioavailability study (Protocol 30) of three nabilone formulations was conducted in four subjects: (1) a nabilone/starch capsule formulation (similar to original formulation); (2) a nabilone/PVP formulation by the

rotary evaporated method (used in the nabilone-prochlorperazine trials - Protocol 20); and (3) a nabilone/PVP formulation (granulation method) which is the formulation proposed for marketing. According to the sponsor, the study shows that the two nabilone/PVP formulations are bioequivalent. This study has been rejected by Dr. Hepp (see Biopharmaceutics review of 5/27/83) as the sample size does not permit adequate power to detect a 20% difference between formulations and the elimination parameters of nabilone and its metabolites are inadequately characterized. Moreover, the dose proportionality study (Protocol 35) does not appear to be satisfactory in fulfilling the bioavailability requirements (Hepp review, 5/27/83). Neither problem is usually considered to be intrinsically serious enough to cause "non-approval" of the drug product. It is my understanding that Biopharmaceutics is willing to negotiate Phase IV bioavailability and dose-proportionality studies.

3. Pharmacology

a. Pharmacodynamics

Nabilone demonstrated antiemetic activity in two preclinical models, carmustine and mechlorethamine-induced vomiting in the cat and cisplatin-induced vomiting in the pigeon. Nabilone did not block apomorphine emesis in the dog. Interestingly, nabilone was 160 times more potent than prochlorperazine against cisplatin-induced vomiting in the pigeon. Thus, either a species difference or a spectrum of action difference is suggested for nabilone versus prochlorperazine.

Nabilone's effect on spontaneous motor activity and general behavior was assessed in the mouse, rat, cat, dog, and rhesus monkey. The general effect across species was depression of motor activity and depression of normal behavior. These data suggest that nabilone will produce sedative effects in human populations.

Identification of the pharmacological class that nabilone belongs to was conducted under the CPDD testing programs

Although nabilone was active in two analgesic screening tests, it was not antagonized by naloxone. In morphine-dependent monkeys undergoing withdrawal, nabilone partially suppressed abstinence. Specifically, retching and vomiting were suppressed. However, other signs of abstinence were not antagonized (e.g., mydriasis). Thus, nabilone was considered non-opioid like.

In the rhesus monkey, nabilone produced ptosis, dozing, mydriasis, ataxia and reduced responsiveness to cage mates and observers. In this regard, it was five times as potent as delta-9-tetrahydrocannabinol (delta-9-THC). A 30-day administration of nabilone revealed increasing tolerance to the behavioral effects. In fact, over a 500-fold increase in the original dose failed to elicit nabilone-like activity. Cross-tolerance to delta-9-THC but not morphine was demonstrated.

There is one preclinical test that is purportedly specific for cannabinoid drugs, the dog static ataxia test. Nabilone and two of its carbinol metabolites were evaluated in this test. Both nabilone and its RRS (6aR, 9S, 10aR) metabolite produced ataxia and body sway at 32 mg/kg, i.v. doses. The SSS (6aS, 9S, 10aS) carbinol metabolite was less active in this test.

b. Pharmacokinetics

The major metabolic transformation of nabilone in all species studied (including man) involves the stereospecific reduction of the 9-keto group to its corresponding carbinols. Nabilone is a racemic (50:50) mixture of two optical isomers, designated RR and SS ketones, which exist in a fixed trans geometry at the 6a, 10a ring junctions. Thus, nabilone is converted to two carbinols, designated the RRS and the SSS carbinols, respectively.

Preclinical studies were conducted in rats, dogs and monkeys using ^{14}C -nabilone to determine its absorption, distribution, metabolism and excretion patterns in these species. In the rat, ^{14}C -nabilone was administered by both oral and intravenous routes. The plasma half-life of total radioactivity was found to be 6 hours following i.v. administration and 20 hours following oral administration.

The ratio of carbinol to nabilone was determined in a separate experiment. Plasma concentrations of "carbinol" were found to be 10 times higher than the parent at 1-, 3-, and 6-hour sampling times. Brain concentrations of the "carbinol" were about 1/2 the plasma concentration.

The feces appeared to be the major excretory route, irrespective of route of administration. However, there was a qualitative difference in that following i.v. administration, biliary excretion of nabilone products occurred as unidentified polar metabolites whereas following oral administration, 50% of the fecal radiocarbon was identified as nabilone. These data indicate that nabilone was incompletely absorbed in the rat.

Oral or intravenous administration of nabilone in the dog resulted in the rapid production of the RRS and SSS carbinol metabolites. Following oral administration, peak plasma levels of nabilone and its carbinol metabolite occurred in two hours. By either route of administration, the ratio of plasma carbinols to nabilone was greater than 4. Further analysis revealed the SSS:RRS ratio to be 5:1. The plasma $t_{1/2}$ after i.v. administration was 1 to 2 hours for the parent and 20 hours for the carbinol metabolites.

Total bioavailability (radioactivity) was calculated to be 25% following oral administration. Nabilone bioavailability was determined to be 7%, indicating extensive biotransformation.

A tissue distribution experiment of orally administered nabilone to a mongrel dog revealed that all radioactivity could be accounted for by nabilone and its carbinol metabolites. (This is not the case in the beagle dog). Analysis of brain tissue from the mongrel dog revealed that the SSS-carbinol was being concentrated in brain tissue as it exceeded the plasma concentration by a four-fold. All the radioactivity in the cerebral cortex and cerebellum was accounted for by the SSS-carbinol.

A tissue distribution study of ^{14}C -nabilone was performed in 3 beagle dogs. Peak plasma levels of nabilone and its SSS-carbinol metabolite accounted for by the RRS metabolites (which could not be determined due to interference by plasma cholesterol) and other unidentified metabolites. The ratio of the peak SSS-carbinol to nabilone was 5:1. Plasma half-lives were determined to be 4.7 hours for nabilone, 12 hours for the SSS-carbinol and 26 hours for "total radioactivity." Animals were sacrificed 24 hours post-nabilone administration and tissues were assayed for nabilone and its RRS and SSS carbinols. The SSS-carbinol levels in the cerebral cortex and cerebellum were 5 times greater than the plasma concentration. The levels of nabilone and its RRS metabolite were below the limits of detection.

In the monkey, single oral doses of ^{14}C -nabilone equivalent to 0.1, 1 and 10 mg/kg were administered. Peak plasma levels occurred at 2 hours at the two lower doses and at 4 hours at the high dose. At the 1 mg/kg dose, nabilone and its SSS-carbinol metabolite accounted for 10 to 15% of the plasma radioactivity. Plasma half lives were calculated to be 1.5 hours for nabilone, greater than 30 hours for the SSS-carbinol and 10 hours for "total radioactivity." At the 10 mg/kg dose, detectable (> 1 ng/ml) plasma concentrations of the SSS-carbinol were not observed. No explanation was offered for this apparently anomalous result.

In a second study, 0.4 mg/kg ^{14}C -nabilone was administered orally to monkeys. At 2 hours, peak plasma radioactivity occurred with nabilone and its SSS-carbinol metabolite accounting for 28% of the peak plasma radioactivity. The plasma half lives were calculated to be 1.5 hours for nabilone, 3.2 hours for the carbinol metabolite and 11 hours for total "radioactivity." Concentrations of radioactivity in the brain measured 24 hours after dosing were in the 1 to 10 ng/g range; the corresponding plasma level was 10 ng/ml of drug equivalents. Neither nabilone nor the SSS-carbinol could be detected in plasma and brain samples taken at 24 hours. Apparently both the parent and its SSS-carbinols are subject to further metabolism.

^{14}C -nabilone (as a co-precipitate with PVP) was administered to two volunteers. The 2 mg dose produced a C_{max} of 10 ng/ml at 2 hours. The half-life of nabilone was calculated to be 2 hours whereas the $t_{1/2}$ of the total radioactivity was 35 hours. Sixty and 24% of the radioactivity were eliminated in the feces and urine, respectively.

A 0.5 mg dose of ¹⁴C-nabilone was administered intravenously to 5 subjects. The recovery of radioactivity from feces and urine was 67 and 22 percent, respectively.

A study was conducted utilizing non-isotopic nabilone (1 mg t.i.d. for 14 days) in 5 subjects. Plasma was analyzed for nabilone and carbinol metabolites by the GC/MS method of Sullivan which has detection limits of 0.4 and 0.8 ng/ml for nabilone and the "carbinol" metabolites, respectively. The "carbinol" levels ranged from 1.3 to 2.1 ng/ml.

A pilot bioavailability study (Protocol 30) was conducted in 4 subjects. This was a 4-period, 4-treatment crossover study. The two formulations used in the clinical trials (nabilone/prochlorperazine and nabilone/placebo) were compared to a nabilone/starch formulations and a reference suspension. Mean nabilone Cmax's were 2.8, 3.8, 1.6 and 5.4 for the four treatments, respectively. Tmax occurred at 1.3, 1.6, 1.4 and 0.7 hours, respectively.

A pilot dose-proportionality study (Protocol 35) was also conducted in 4 volunteers. Deuterated nabilone was added to a nabilone suspension and 1, 2, and 3 mg capsules of nabilone. Mean nabilone Cmax values were 4.0, 1.5, 3.7, and 3.5 ng/ml while mean nabilone Tmax values were 0.6, 2.3, 1.8, and 4.1 hours, respectively. Based on mean AUC nabilone/AUC D-6 nabilone ratio analysis, dose-proportionality was not demonstrated.

c. Toxicology

Subacute and chronic toxicity studies of nabilone were performed by the oral and i.v. routes in the rat and dog and by the oral route in the dog and monkey, respectively. In the rat, nabilone produced catatonia and hyperirritability to touch following oral administration. These signs rapidly resolved, suggesting tolerance to certain CNS effects of nabilone.

Oral administration of nabilone to beagle dogs in a 92-day study produced ataxia. Tolerance developed to this effect by the end of the second dosing week.

A second oral toxicity study of nabilone (doses of 0.5, 1.0, and 2.0 mg/kg) in dogs, planned for a one-year dosing exposure, was terminated at 7 months due to cumulative toxicity. Two low-dose, 6 mid-dose, and 7 high-dose dogs died or were sacrificed in a moribund condition. Convulsions often preceded death. It was noted that animals usually appeared healthy until near death. (These data caused the interruption of clinical trials in 1979. The agency's position on resumption of clinical trials was that (1) a one-year monkey study should be performed; and (2) carbinol metabolite studies should be performed in species such as the rat and the dog - Kartzinel to Lilly letter - 4/2/80

Subsequently, a five-day i.v. toxicity study comparing nabilone and its SSS-carbinol metabolite was performed in beagle dogs. Signs

of CNS depression were noted with both drugs. Plasma samples taken from dogs in both groups revealed that SSS carbinol levels were about twice as high in the SSS carbinol-treated group.

A one-year toxicity study of nabilone was performed by nasogastric administration in rhesus monkeys. Sedation and hypoactivity were identified at doses of 0.5 and 2.0 mg/kg. Tolerance developed to the CNS effects. No deaths were observed.

In summary, the major toxicologic finding in the subacute and chronic toxicity studies was the cumulative toxicity of nabilone in the beagle dog. It was the sponsor's hypothesis that the SSS carbinol (which is formed in the greatest quantities in the dog relative to the rat, monkey and man and is sequestered in the dog's central nervous system) was the toxic moiety. The evidence for this is inferential insofar as the toxicity is observed in the species with the highest conversion to SSS carbinol and not observed in 3 other species in which SSS carbinol levels are far lower. There was an agreement reached by Dr. Contrera with Lilly toxicologists on 5/7/80 that the carbinol metabolite needed further evaluation but could be done "after the NDA process." This should be a formal request if and when an approvable letter is issued.

A secondary issue observed in the animal studies is the development of tolerance to the CNS depressant effects of nabilone. This was confirmed in a pilot study in humans - (See "IND protocol #2" in Vocci drug abuse consulting review of 11/23/82). Whether tolerance develops to the antiemetic effect of nabilone or other side effects is an important issue although the episodic nature of cancer chemotherapy makes it unlikely that a diminished drug effect would occur across treatment episodes. It is possible, however, that tolerance could develop within treatment episodes, especially those lasting more than 5 days.

In reproduction and teratology testing, nabilone decreased food consumption and maternal weight gain. This was linked to a decrease in litter size and an increase in the number of still births. Pup survival rates in nabilone-treated groups were reduced. This may be a result of both maternal and pup characteristics. The dams produced less milk, apparently due to a nabilone influence on prolactin release. The pups were hypothermic which may have been due to an intrauterine effect of nabilone in concert with compromised nutrition.

Nabilone was not teratogenic in standard assay procedures in the rat and rabbit at doses greater than 200 times the proposed human dose.

Nabilone did not produce effects consistent with genetic mutation in the Ames test, sister chromatid exchange test, DNA repair test in rat hepatocytes, dominant lethal test in rats, and micronucleus test in polychromatic erythrocytes in rat bone marrow.

Carcinogenicity testing with nabilone has not been initiated. This is consistent with the agency policy of a waiver of carcinogenicity testing of anticancer drugs.

4. Clinical background

a. Literature reports

The sponsor has supplied published reports on the chemistry, pharmacology and clinical effects of nabilone. There are four published reports that summarized the results of individual investigators in either the nabilone-prochlorperazine multi-centered trial (Protocol 20) or an open study of nabilone in chemotherapy patients. The reports will be described here and reviewed in greater depth in Section 5 of this review.

- (1) Herman, T.S., Einhorn, L.H., Jones, S.E., Nagy, C., Chester, A.B., Dean, J.C., Furnas, B., Williams, S.D., Leigh, S.A., Dorr, R.T., and Moon, T.E.. Superiority by Nabilone Over Prochlorperazine as an Antiemetic in Patients Receiving Cancer Chemotherapy. N. Eng. J. Med. 300: 1295-1297, 1979.

The authors reported the results of a randomized, double-blind crossover comparison of the antiemetic effect of nabilone versus prochlorperazine in patients receiving cyclic, combination chemotherapy for solid tumors. The studies were performed at the University of Arizona and the Indiana University School of Medicine.

One hundred and fifty-two patients (152) patients were admitted to the study. Fifty-two (52) patients were treated as outpatients
100 were treated as

inpatients. The major chemotherapeutic and antiemetic regimens were as follows: (1) 70 patients with testicular carcinoma who received cisplatin (daily for 5 days), vinblastine and bleomycin also received nabilone for 5-1/2 days; (2) 12 patients treated for non-Hodgkin's disease who received cyclophosphamide, doxorubicin, vincristine and prednisone also received nabilone for 1-1/2 days; and (3) 11 patients with Hodgkin's disease who received nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) also received nabilone for 1-1/2 days.

Nabilone was supplied in 1 mg capsules.

patients received either 2 mg of nabilone or 10 mg of prochlorperazine every 8 hours beginning two doses prior to chemotherapy. patients were treated with identical doses every six hours beginning 30 minutes before chemotherapy.

One hundred and thirteen (113) patients completed the crossover. Dropouts were encountered for a variety of reasons: disease progression, unacceptable side effects, insufficient data collected and anticipatory vomiting prior to chemotherapy. Of the five nabilone-treated patients who dropped out due to unacceptable side effects, two had noteworthy adverse experiences: one had orthostatic hypotension which required medical treatment and the other had visual hallucinations and "depersonalization."

Efficacy was evaluated by daily patient ratings of severity of nausea and incidence of vomiting. At the end of each cycle, patients were asked to compare nausea and vomiting with their pretreatment (previous chemotherapy) levels. Scoring was done on a graded scale; i.e., less than 50% response equaled no response, 50% less nausea and vomiting was scored as a partial response, and a complete response was defined as a total absence of nausea and vomiting during a treatment period. At the end of the trial, patients were asked whether they preferred one antiemetic over the other.

Nabilone was superior to prochlorperazine in every efficacy category. Nine (9) patients (8 percent) had a complete response to nabilone. No patient receiving prochlorperazine had a complete response. Eighty-one (81) patients (72%) of the nabilone group had a partial response compared to 36% of the prochlorperazine group ($p < 0.001$, McNemar's test). Additionally, patients recorded less vomiting throughout the treatment cycle when they received nabilone ($p < 0.001$). Further, statistically significant reductions in nausea severity were recorded ($p < 0.05$ to 0.001) for nabilone versus prochlorperazine across treatment days. Finally, 75% of the patients preferred nabilone whereas 18% chose prochlorperazine as the antiemetic of choice ($p < 0.001$).

Common side effects included somnolence, dizziness and dry mouth. Nabilone specific side effects included euphoria (16%), hallucinations (3%), orthostatic hypotension (1%). Even with commonly occurring side effects, those occurring with nabilone were more severe and occurred with a higher incidence.

- (2) Steele, N., Gralla, R.J., Braun, W.W., Jr. and Young, C.W. Double-blind Comparison of the Antiemetic Effects of Nabilone and Prochlorperazine on Chemotherapy-Induced Emesis. Cancer Treat. Rep. 64: 219-224, 1980.

This report summarizes the experience of 31 patients at Memorial Sloan Kettering who participated in a randomized double-blind crossover comparison of nabilone (2 mg) versus prochlorperazine (10 mg) during two successive, identical courses of chemotherapy. Of

note in this report is the analysis of efficacy of the antiemetic as a function of the emetic strength of the chemotherapeutic stimulus. The emetic stimuli administered were (in order of high to low) high dose cisplatin, low dose cisplatin, and mechlorethamine, streptozotocin, actinomycin D or DTIC.

Efficacy parameters assessed the severity of nausea, the frequency and duration of vomiting, and patient preference for either antiemetic.

Safety analysis included a CBC, urinalysis, SMA-12, and electrocardiogram in hospitalized patients during treatment with both antiemetics. Supine and standing blood pressure were monitored every 4 hours during waking hours. Outpatients had a CBC, platelet count, and SMA-12 performed before receiving each drug. The report states that baseline urinalysis and ECG were available. Side effect incidence was tabulated for both patient groups during both antiemetic treatments.

Perception of the duration of nausea varied with the emetic stimulus; i.e., high dose cisplatin low dose cisplatin other regimens. The severity of nausea was more linked to whether the patients were inpatients or outpatients, nausea being more severe in outpatients on comparable treatment regimens.

The duration and severity of vomiting were greater in outpatients who received "other chemotherapy." Neither antiemetic was particularly effective in high dose cisplatin (HD) courses. Emesis was well-controlled in only 2 of 15 courses of chemotherapy on nabilone and 2/15 courses on prochlorperazine. Median duration (but not frequency) of low dose (LD) cisplatin-induced vomiting was reduced more by nabilone than prochlorperazine. Patients receiving "non-cisplatin" courses had reduced frequency and severity of vomiting episodes on nabilone.

Patient preference was analyzed as a function of antiemetic treatment and the order of drug administration. Patients in the LD cisplatin group had a 60% preference for nabilone (20% had no drug preference). Patients in the "other chemotherapy" group expressed a 75% preference for nabilone. An overall preference was recorded for nabilone but this result did not attain statistical significance ($p > 0.05$, binomial test). Order of administration did not affect preference.

One interesting point observed was that 13 of 16 patients correctly guessed they were receiving nabilone ($p < 0.05$, binomial test). This raises the issues of side effect differences unmasking the study blind as well as influencing patient preference and response.

Side effect incidence was lower for prochlorperazine and thus may have been more tolerable. Drowsiness was the only significant side effect that occurred (35% incidence). Nabilone, on the other hand, produced a high degree of somnolence (47%), dizziness (36%) and dry mouth (25%). Side effects were less annoying to the hospitalized patients.

Four patients withdrew from the study due to intolerable nabilone-related side effects. These reactions were characterized as severe dizziness, decreased ability to concentrate, lack of coordination, and dysphoria. One of the dysphoric patients experienced hallucinations, time-space distortion and dyspnea.

Eight patients received further nabilone on an open label basis for one to four more chemotherapy regimens. There was no evidence of a diminished therapeutic effect or reduced side effect incidence.

The authors commented on the low incidence of postural hypotension noted in comparison to other studies. The explanation offered was that this was due to a lack of blood pressure monitoring in the outpatient group.

- (3) Einhorn, L.H., Nagy, C., Furnas, B., and Williams, S.D. Nabilone: An Effective Antiemetic in Patients Receiving Cancer Chemotherapy. *J. Clin. Pharmacol.* 21: 645-655, 1981.

The efficacy portion of this trial has previously been discussed under Herman *et al*, *N. Engl. J. Med.* 300: 1295-1297, 1979. However, one difference in drug administration was cited by the authors. Initially the study drug was administered 30 minutes prior to initiation of chemotherapy; however, the last 44 patients inducted into the protocol received the drug starting 12 hours prior to chemotherapy. There was no explanation given for the change of timing of antiemetic drug administration.

Several observations described are worth noting. The first is that drug preference and antiemesis do not necessarily covary; i.e., 6 patients who chose nabilone experienced less emesis with prochlorperazine and 9 patients who preferred prochlorperazine actually had less emesis on nabilone therapy. The second observation is that the nabilone "high" (not defined by the investigators to the subjects) was dose-related. Twenty of fifty-two patients (38%) receiving 2 to 4 mg/day experienced a "high" while 20 of 28 (71%) of the patients who took 6 to 8 mg/day reported this effect. The third effect of note is that both study drugs produced hypotension in 70 of 80 patients. Nabilone and prochlorperazine were about equivalent in producing blood pressure decreases in the 20 to 29 mmHg range but

nabilone appeared to cause more hypotensive drops of 30 mmHg or greater [36/70 (51%)] than prochlorperazine [20/70 (29%)]. No treatment was needed for the hypotension and chemotherapy proceeded without interruption.

Three patients had syncopal episode; two were attributed to nabilone while the other was prochlorperazine associated.

- (4) Herman, T.S., Jones, S.E., Dean, J., Leigh, S., Dorr, R., Moon, T.E. and Selman, S.E. Nabilone: A potent cannabinol with minimal euphoria. *Biomedicine* 27: 331-334, 1977.

The authors reported the effects of an open design trial of nabilone in 13 patients undergoing cyclic chemotherapy who were refractory to prochlorperazine. Six (6) of the patients received 1 mg every 8 hours and the remaining 7 patients received 2 mg every 8 hours. Nabilone (2 doses) was administered prior to chemotherapy initiation and continued for 5 days. Patients were analyzed as a function of dose per body surface area. The low dose (LD) group received 1.6 to 2.0 mg/m²/day and the high dose (HD) group received 2.6 to 3.6 mg/m²/day.

There was evidence of a dose-effect relationship in that HD patients reported less nausea and vomiting than the LD group. Three patients (2H, 1LD) requested nabilone discontinuation after the first day of chemotherapy due to somnolence in two patients and decreased ability to concentrate in one patient. Orthostatic changes in blood pressure were greatest on day two or three. The most marked change in blood pressure recorded was a drop of 38/22 mmHg in one patient. Postural dizziness occurred in 8/13 patients.

The authors commented that the dosing schedule did not produce marijuana-like "highs" and thus some separation of antiemetic and euphoric effects was noted. However, this may be due to a failure to recognize subtle effects which constitute the "high" on the parts of both investigators and patients. Somnolence, dizziness, decreased concentration, decreased coordination, distortions of time-space perception, feelings of dissociation and affective changes (euphoria, dysphoria, anxiety, panic, transient psychosis) are all symptoms of marijuana intoxication. Older patients who lack prior cannabis experience might not associate some, if not most, of the symptoms with a "high" or euphoriant effect. These same symptoms were reported by patients in varying degrees, thus suggesting coexistence of antiemetic and CNS intoxication associated with nabilone. It may be that only the affective component was being recognized as a "high" or euphoriant effect.

N-18677-4

d. Global comments:

Nausea and vomiting associated with cancer chemotherapy are not clinically trivial events. Repeated vomiting can produce chloride depletion, metabolic alkalosis, dehydration, and hypokalemia. Some of these effects (chloride depletion, metabolic alkalosis, and to some extent dehydration) are a direct consequence of vomiting or inability to maintain an oral fluid intake, whereas the maintenance of the alkalosis and the production of hypokalemia are a result of renal compensatory mechanisms. Other rarer consequences include gastric mucosa rupture and skeletal fractures. (See Penta, J., Poster, D. and Bruno, S. The Pharmacological Treatment of Nausea and Vomiting Caused by Cancer Chemotherapy: A Review. In Antiemetics and Cancer Chemotherapy, ed. J. Laszlo, Williams and Wilkins Press, Balto, Md., 1983).

These facts may have, in part, led to increased sensitivity on the part of oncologists to alleviate drug-induced side effects of chemotherapy. Also, it has been said that this resulted from the current advances in chemotherapy which now can prolong life or even affect cures. This change is reflected in the scientific literature on antiemetic trials. Penta et al (ibid) reviewed antiemetic trials associated with chemotherapy reported in the medical literature from 1960 to 1981. Of the 57 drug trials reviewed, 41 took place in the years 1979 through 1981. Of the studies reviewed, 25/27 used prochlorperazine. It was effective in 13/25 (52%) of the trials. This strongly suggests, among other things, that prochlorperazine is only moderately effective as an antiemetic, not surprising when one considers the heterogeneity of the emetogenic stimuli associated with the various cancer chemotherapy agents.

The relatively recent development of interest in antiemetic drug trials has led many investigators to use various rating scales for nausea and vomiting. In short, there are no uniform criteria for measuring nausea and vomiting. The vomiting scales usually quantify the number of emetic episodes, retching, and, sometimes, the volume of emesis. Such scales have obvious face validity. Other vomiting scales ask patients to determine if a 50% (or greater) reduction in vomiting occurred in comparison to the previous chemotherapy. Responses in such trials may quantify antiemesis as complete, greater than a 50% reduction, or less than a 50% reduction.

The rating scales for nausea are somewhat more problematic. Many investigators have chosen to arbitrarily make up their own nausea rating scales. Some assess nausea alone on a graded basis while others assess the patient's nausea and vomiting simultaneously. To my knowledge, none of these scales have been externally validated. [It may be possible to use a physiological marker of nausea in future drug trials. Rowe et al reported that administration of sub-emetic doses of apomorphine to 10 subjects caused a 60-fold increase in plasma vasopressin (Kidney Int. 16: 729, 1979). Thus, an effective antinauseant may reduce or completely block the elevation of plasma vasopressin.]

While the non-uniform unvalidated rating scales are undesirable and may, in themselves, lead to non-uniform results across trials, they represent an area of clinical pharmacology too new to reach a consensus as to which rating scales (if any) have greater validity.

5. Clinical Studies - Well-Controlled Studies

There are four studies which can be considered well-controlled that could demonstrate efficacy. Protocols 7, 9, and 20 compare the antiemetic effects of nabilone versus prochlorperazine in patients undergoing cancer chemotherapy. In order for nabilone to demonstrate efficacy in these trials, superiority over prochlorperazine needed to be demonstrated. Protocol #28 is a comparison of nabilone versus placebo in patients undergoing cancer chemotherapy. The active control studies will be reviewed first.

a. Protocol #20:

(1) Background:

This was a multicentered trial conducted at three sites. The investigators were , (#301), (#302) #306). The study was interrupted in January, 1979 after 10 patients were enrolled. Seven patients in this study were considered evaluable. However, the statistical analysis demonstrated a significant investigator by residual interaction on vomiting parameters. When the emesis data from investigator #306 were excluded from analysis, the composite analysis of investigators 301 and 302 did not yield a significant investigator by residual interaction.

The sponsor analyzed the efficacy variables from each center in addition to analyzing the composite results. I will review the results of each center and then the composite results.

(2) Study design:

This was a double-blind, randomized, crossover study comparing the safety and effectiveness of nabilone versus prochlorperazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents in two cycles of chemotherapy. Patients were randomly assigned to receive either nabilone or prochlorperazine during the first cycle of chemotherapy and the other drug during the second cycle. The study drug was administered throughout the chemotherapy cycle, which usually lasted 1 to 5 days. Chemotherapy cycles were usually given 3 to 6 weeks apart.

Dosing began on the evening before chemotherapy and continued with administration of study drug 1 hour before and 12 hours thereafter until 24 hours after the cessation of chemotherapy. The dose of nabilone was one (2 mg) capsule, b.i.d. The dose of prochlorperazine was one 10 mg capsule which was identical in appearance to the nabilone capsule.

Inclusion criteria included the following: (1) male or female cancer patients older than age 12 who had received cyclic chemotherapy known to have caused nausea and vomiting during at least two previous consecutive chemotherapy cycles; (2) chemotherapy regimens would remain the same for two consecutive cycles; and (3) written informed consent would be obtained from patients or parental guardian.

Patients were to be excluded from study participation if they had cardiovascular disease, psychotic episodes of a recurring nature or were regular users of marijuana. Females were to be excluded if they were pregnant or not using an appropriate method of contraception.

Efficacy and safety evaluations were recorded on a 24-hour basis. At the completion of the crossover, the patient chose a preferred study drug and the investigator recorded his global impressions of the efficacy and safety of each antiemetic treatment. Patients had the option of continuing with nabilone or an open label basis.

There were three patient-related efficacy variables and two investigator-rated variables during each cycle. Patients recorded the number of vomits per day, the severity of nausea (none, mild, moderate, severe), and food intake (none, less than usual, average for me, more than usual). Investigators rated efficacy (very good, good, fair, poor, and very poor) and the severity of adverse effects [none, did not interfere with patient's functioning, significantly interfered with patient's functioning, (and) outweighed the therapeutic effect.]

Safety parameters included a medical history and physical examination, SMA 12/60, hematology and urinalysis for each patient prior to each cycle of drug administration, including any open label studies. Laboratory tests were to be repeated prior to the next cycle of chemotherapy after the patient had completed the "study drug" portion (2 cycles) of chemotherapy.

Patients recorded adverse reactions on a daily questionnaire which noted the presence of euphoria (a high) and asked to note any other treatment emergent adverse experience.

Patients were randomized according to a pre-determined schedule. The investigator had each patient's drug code in a sealed envelope and referred to it only if he deemed it medically necessary.

In addition to the aforementioned, patient's primary cancer diagnosis, age, sex, intercurrent illnesses, and concomitant medications were recorded.

The following decision rules were used to consider a patient "evaluable": (1) the patient was required to have one or more evaluable days on each cycle; (2) "evaluable" days were the number of days of chemotherapy in which the study drug was administered and "no protocol violations" occurred. The lesser of the two numbers, that is, the number of evaluable days for cycle 1 or the number of evaluable days for cycle 2, was used in the crossover analysis.

Patient rated efficacy variables (vomiting, nausea, food intake) were considered independently when evaluability was assessed. Thus, missing data for one parameter did not exclude the patient's other data from the analysis.

The following situations were deemed "protocol violations":

- (a) a second antiemetic was given other than the study drug assigned by the randomization schedule;
- (b) the study drug was not administered concomitantly with chemotherapy;
- (c) the specific dose of antiemetic, as called by the study protocol was not given prior to chemotherapy; and
- (d) A different cancer chemotherapy regimen was used during the two cycles of chemotherapy on the crossover. Any one of these violations was sufficient to exclude a patient from the efficacy analysis.

(3) Statistical analysis:

Individual investigator results were analyzed for comparability of the sequence groups in both evaluable and unevaluable patients with respect to chemotherapy, prior chemotherapy, sex, and age. When the composite analysis was performed, comparability of sequence groups in both evaluable and unevaluable patients was determined with regard to cancer diagnosis, chemotherapy, prior chemotherapy, sex, age and interaction effects (e.g., investigator by evaluability interaction).

Efficacy and safety data were first described using measures of central tendency and dispersion. If a patient's daily score on a particular variable was missing or unevaluable (continuous vomiting) on one cycle, the alternative cycle's score was eliminated to achieve balance. However, the sponsor used all scores in the non-parametric and contingency analyses.

Data were analyzed using a non-parametric technique appropriate for crossover analysis (Koch, G.G., *Biometrics*, June, 1972, p. 577-584). Hypotheses concerning direct effects (treatment), crossover effects (residuals) and period effects (cycle) were analyzed using a Wilcoxon two-sample test. The significance level for testing of residuals was $\alpha = 0.10$. If no residual effect occurred, treatment differences were evaluated combining both cycles.

Data were also analyzed for each cycle using the Wilcoxon two-sample test. If a significant residual effect occurred, cycle 1 data were evaluated for treatment effects.

A categorical analysis for each of the efficacy and safety variables examined treatment and cycle effects. Patient preferences were also analyzed by categorical analysis. Differences in response were grouped into three categories (nabilone better, prochlorperazine better, same). Frequencies were analyzed using an exact method for comparing matched proportions in a crossover design (Gart, J.J. *Biometrika* 56(1): 75-80, 1979). Frequency analysis by cancer chemotherapy dose and/or regimen was also performed. Fisher's Exact Test was used in these tests.

The sponsor also analyzed all cycle 1 patients (both evaluable and unevaluable) using the Wilcoxon two-sample test.

Blood pressure (systolic and diastolic) responses were analyzed by drug for increases versus decreases by a sign test. The test drugs were compared using a sign-test on the pairwise differences from baseline.

All data were analyzed for significance using two-tailed tests.
Reviewing statistician's comments (E. Nevius review):

Dr. Nevius commented that the analysis of variance on ranked data had been discussed in the statistical literature, but had not previously been applied to this situation. He did not imply that it was invalid or inappropriate in his review. I communicated with him further on the subject and was told that he felt the analysis of variance was appropriate. Further, Dr. Nevius concluded that the frequency analysis supported the analysis of variance results.

(4) Individual Investigators:

Investigator 301

Patients in this study were male and female, in- and outpatients, between the ages of 19 and 68 years old. Sixty-seven patients, 43 male and 24 female, enrolled in the study. The diagnostic frequency is given in Table 1.

Table 1: Frequency of Cancer Type in Study Population

<u>Type</u>	<u>Number</u>	<u>(%)</u>
lung	30	(44.8)
melanoma	7	(9)
bladder	5	(7)
colon	5	(7)
testicle	5	(7)
other	5	(21)

The lung cancer patients received cisplatin and vindesine. The doses of cisplatin were categorized as being above 100 mg/m² or 100 mg/m² or below. Patients were also subgrouped as to whether or not they received cisplatin. Melanoma patients were treated with cyclophosphamide and dacarbazine. Other chemotherapeutic agents administered were adriamycin, chlorambucil, dactinomycin, nitrogen mustard, procarbazine, streptozotocin, vincristine and vinblastine. Within the exception of two patients (#7 and 19), multiple chemotherapeutic agents were administered only on day 1 of the treatment cycle.

Thirty-two (32) of 67 patients enrolled were considered evaluable. Thirteen (13) patients were enrolled but discontinued when the clinical trials were suspended in 1979. The reasons for termination of the study subjects are given in Table 2.

Table 2:
Reasons for Early Terminations
(Sponsor's Table 10, Vol. 1.10, pg 110)

<u>Reason</u>	<u>No. of Patients</u>	<u>Patient Nos.</u>
Drug-related (nabilone)	3	9,28,36
Lack of efficacy (nabilone)	3	11,30,35
Lack of efficacy (prochlorperazine)	3	5,41,43
Lack of efficacy (nabilone and prochlorperazine)	1	39
Adverse experiences (unknown cause)	2	14,52
Protocol violation	2	27,54
Death due to cancer	1	6
Study suspended	<u>13</u>	34,37,57-61, 64-66,68,69, 71,72
Total	28	

Additionally, 7 patients were considered unevaluable due to protocol deviations. These were mostly related to incomplete dosing on the second cycle of the crossover. The patient numbers were #4,7,22,33,38,44, and 50.

Of the 13 patients terminated due to the suspension of the trial, 7 appeared to have data "evaluable" for cycle 1 analysis. However, only 54/67 patients were tabulated in the cycle 1 analysis of "all" patients (vide infra). As no superiority of nabilone over prochlorperazine was evident in this trial, any bias entered in the results could possibly have made nabilone look less effective. However, my own ranking of the data suggests that nabilone would have, if anything, looked better had these data been entered; i.e., N (0 vomits), P (5 vomits), N (15 vomits), N (19 vomits), N (continuous vomiting), P (continuous vomiting), P (continuous vomiting).

The evaluability of patients as a function of sequence and cancer chemotherapy is displayed in Table 3.

Table 3:
Cancer Chemotherapy By Evaluability and Sequence Group
(Sponsor's Table 1, Vol. 1.10)

<u>Cancer Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	10	11	21	17	9	26
Other combinations without cisplatin	<u>3</u>	<u>8</u>	<u>11</u>	<u>3</u>	<u>6</u>	<u>9</u>
Total	13	19	32	20	15	35

The data may also be displayed as a function of evaluable patients/dose of cisplatin (Table 4).

Table 4: Evaluable Patients per Cisplatin Dose per Sequence Group (Cycle)

<u>Cisplatin Dose</u>	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>
High (> 100 mg/M ²)	8	5	13
"Low" (≤ 100 mg/M ²)	2	6	8
None	<u>3</u>	<u>8</u>	<u>11</u>
Total	13	19	32

Statistical analysis inferred a significant group by chemotherapy interaction ($p < 0.03$). It should also be noted that the doses of cisplatin in this study are for higher than those used by Einhorn (#302, who used 20 mg/m²).

The efficacy results are reported in terms of mean and standard deviation for both drugs as a function of cycle 1, cycle 2 and both cycles (Table 5).

Table 5:
Descriptive Statistics of
Daily Averages and Investigator's Global Impressions
(Sponsor's Table 1A, Vol 1.10, Appendix E, pg 277)

	Daily Averages			Investigator's Global Impressions	
	Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1					
Nabilone Mean	10.92	1.46	1.23	2.38	0.85
S.D.	11.72	0.88	0.44	1.26	0.90
n	12	13	13	13	13
Compazine Mean	5.33	1.68	1.00	2.89	0.65
S.D.	5.22	0.89	0.75	1.59	0.60
n	15	19	19	19	19
Cycle 2					
Nabilone Mean	5.40	1.32	1.11	2.26	1.00
S.D.	5.28	0.82	0.88	1.45	0.94
n	15	19	19	19	19
Compazine Mean	11.25	1.77	1.00	3.69	0.31
S.D.	13.58	1.01	0.71	1.65	0.48
n	12	13	13	13	13
Both Cycles					
Nabilone Mean	7.85	1.38	1.16	2.31	0.94
S.D.	8.99	0.83	0.72	1.35	0.91
n	27	32	32	32	32
Compazine Mean	7.96	1.72	1.00	3.22	0.50
S.D.	10.08	0.92	0.72	1.64	0.57
n	27	32	32	32	32

These data suggest an equivalence of nabilone to prochlorperazine with respect to vomiting and food intake. Nabilone may have a salutary effect on nausea. Investigator rated efficacy was noted slightly better for nabilone. However, overall adverse events were rated higher on nabilone. This last observation suggests the study blind may have been broken by the investigator recognizing nabilone-related side effects.

The non-parametric analysis of variance is shown in Table 6.

Table 6:
Non-Parametric Crossover Analysis on Ranks
(Sponsor's Table 2, Vol 1.10, Appendix E, pg 279)

	<u>Seq. Gp. 1</u>		<u>Seq. Gp. 1</u>		<u>Z-value</u>	<u>P-value</u>
	<u>n</u>	<u>Mean Rank</u>	<u>n</u>	<u>Mean Rank</u>		
Residual Effect						
Freq. of Vomits	13	17.27	19	15.97	0.40	.500
Sev. of Nausea	13	17.73	19	15.66	0.63	.500
Food Intake	13	17.62	19	15.74	0.58	.500
Efficacy	13	18.58	19	15.08	1.06	.291
Adverse Effects	13	14.15	19	18.11	-1.15	.250
Treatment Effect						
		(N-C)*		(C-N)*		
Freq. of Vomits	13	15.81	19	16.97	-0.33	.500
Sev. of Nausea	13	12.46	19	19.26	-2.00	.046
Food Intake	13	18.50	19	15.13	1.02	.309
Efficacy	13	12.08	19	19.53	-2.19	.029
Adverse Effects	13	20.15	19	14.00	-1.84	.066
Cycle Effect						
Freq. of Vomits	13	16.42	19	16.55	-0.02	.500
Sev. of Nausea	13	15.92	19	16.89	-0.27	.500
Food Intake	13	17.50	19	15.82	0.52	.500
Efficacy	13	14.69	19	17.74	0.89	.378
Adverse Effects	13	17.42	19	15.87	0.48	.500

*N-Nabilone, C-Compazine

Nabilone was marginally superior ($p = .046$) to prochlorperazine on the severity of nausea scale. Investigator-rated efficacy was also superior for nabilone ($p = 0.29$). Additionally, adverse effects were rated almost significantly higher ($p = .066$) for nabilone. The crossover frequency analysis is shown in Table 7. These corroborate the results in Table 6 with respect to the nausea and investigator-rated efficacy.

Table 7:
Crossover Frequency Analysis
(Table 4, Sponsor's Analysis, Vol 1.10, Appendix E, pg 281)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits					
Nabilone Better	6	5	11		
Same	1	5	6	.500*	.500
Compazine Better	6	9	15		
Total	13	19	32		
Severity of Nausea					
Nabilone Better	6	6	12	.500	.063
Same	5	12	17		
Compazine Better	2	1	3		
Total	13	19	32		
Food Intake					
Nabilone Better	4	6	10	.500	.461
Same	8	8	16		
Compazine Better	1	5	6		
Total	13	19	32		
Investigator's Global Impressions					
Efficacy					
Nabilone Better	9	9	18	.500	.054
Same	2	5	7		
Compazine Better	2	5	7		
Total	13	19	32		
Investigator's Global Impressions					
Adverse Effects					
Nabilone Better	2	4	6	.500	.229
Same	5	8	13		
Compazine Better	6	7	13		
Total	13	19	32		
Patient's Preference					
Nabilone Better	7	13	20	.500	.130
Same	1	2	3		
Compazine Better	5	4	9		
Total	13	19	32		

*From corrected Chi-square test

The frequency analysis as a function of chemotherapy group is presented in Table 8. Nabilone appears somewhat better against cisplatin-induced nausea but clearly superior against non-cisplatin regimens. Patient preference is equal in the cisplatin groups but clearly superior in the other group. It appears that nausea rating and patient performance are highly correlated. Further, investigator-rated efficacy may also be keyed on nausea.

Table 8
Frequency of Patients by Chemotherapy Groups
(Table 6, Sponsor's Analysis, Vol 1.10, Appendix E, pg 283)

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=21) -</u>	<u>Other than Cis-Platinum (n=11)</u>	<u>Total</u>
Freq. of Vomits			
Nabilone Better	6	5	11
Same	4	2	6
Compazine Better	11	4	15
Severity of Nausea			
Nabilone Better	6	6	12
Same	12	5	17
Compazine Better	3	0	3
Food Intake			
Nabilone Better	6	4	10
Same	10	6	16
Compazine Better	5	1	6
Investigator's Global Impressions			
Efficacy			
Nabilone Better	9	9	18
Same	6	1	7
Compazine Better	6	1	7
Investigator's Global Impressions			
Adverse Effects			
Nabilone Better	5	1	6
Same	10	3	13
Compazine Better	6	7	13
Total	13	19	32
Patient's Preference			
Nabilone Better	10	10	20
Same	3	0	3
Compazine Better	8	1	9

The analysis of data from "all" cycle 1 patients is presented in Table 9. It should be noted that there are missing data for both nabilone and compazine groups with the frequency of vomiting data. The missing data may reflect patients who vomited continuously during the chemotherapy cycle. There were no significant differences observed with the efficacy variables. However, there was a trend toward superior nabilone efficacy ($p = .139$) and greater adverse effects attributed to nabilone ($p = .052$).

Table 9:
Descriptive Statistics and Test Results
Cycle 1 - All Patients
(Table 7, Sponsor's Analysis, Vol 1.10, Appendix E, pg 26)

	Freq. of Vomits	Severity of Nausea	Food Intake	Investigator's Global Impressions	
				Efficacy	Adverse Effects
Nabilone Mean	12.58	1.82	1.00	2.67	0.93
S.D.	12.55	1.02	0.68	1.33	0.73
n	24	28	27	27	27
Median	9.00*	2.00	1.00	2.00	1.00
Compazine Mean	10.81	1.81	0.88	3.30	0.52
S.D.	13.91	0.96	0.77	1.56	0.64
n	21	27	26	27	27
Median	8.50*	2.00	1.00	4.00	0.00
Parametric Analysis					
Rank Nabilone	28.34*	28.32	28.44	24.35	31.69
Compazine	28.66*	27.67	25.50	30.65	23.31
Z-value	0.08	-0.14	-0.69	1.48	-1.95
P-value	.500	.500	.493	.139	.052

*n = 28

Investigator 302

Patients enrolled in this study were male, female, in- and outpatients between the ages of 17 and 64. Forty-nine patients, 39 male and 10 female, were enrolled. The diagnostic frequency is given in Table 10.

Table 10: Frequency of Cancer Type in the Study Population

<u>Type</u>	<u>Number</u>	<u>(%)</u>
Testicular	32	(65)
Breast	7	(14)
Other	10	(21)

The 32 patients with testicular cancer were treated with a 5-day regimen of cisplatin (20 mg/M²). Bleomycin and vinblastine were usually administered concomitantly on the first day of the chemotherapy cycle. The seven breast cancer patients were treated with adriamycin, cyclophosphamide and 5-fluorouracil. Patients treated with cisplatin did not have to meet the criteria of two previous, consecutive vomiting episodes.

Thirty-six (36) of 49 patients enrolled were considered evaluable. Of the evaluable patients, 21 (58%) were in treatment group 1 (nabilone during 1st chemotherapy cycle) while 15 (42%) were in treatment group 2 (compazine during 1st chemotherapy cycle). The reasons for termination of the 13 patients is given in Table 11 below.

Table 11: Reasons for Early Termination

<u>Reason</u>	<u>No. of Patients</u>	<u>Patient Nos.</u>
Lost to follow up	8	15, 19, 38, 45, 47, 52, 53, 54
Protocol violation	4	2, 13, 25, 41
Adverse reaction	1	46

(Note: I assigned different termination reasons for patients 13 & 53)

Thirty (30) of the 45 patients in the trial received concomitant medications. The most common medication regimen was Colace, Flurazepam and an analgesic (Darvon, Tylenol with Codeine or Demerol). None of these medications is known to have antiemetic effects. No patient received any glucocorticoids (prednisone, dexamethasone, etc.). This last comment may be of importance as dexamethasone has recently been reported to have antiemetic efficacy in non-cisplatin chemotherapy regimens (NEJM, 9/6/84).

The evaluability of patients as a function of sequence and cancer chemotherapy is displayed in Table 12:

Table 12:
Cancer Chemotherapy By Evaluability and Sequence Group
(Table 1, Sponsor's analysis, Vol. 1.11, p. 6)

<u>Cancer Chemotherapy*</u>	<u>Evaluable</u>			<u>Evaluable</u>		
	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	13	10	23	4	7	11
Other combinations without cisplatin	<u>8</u>	<u>5</u>	<u>13</u>	<u>2</u>	<u>0</u>	<u>2</u>
Total	21	15	36	6	7	13

The frequency of cancer types was evenly distributed across sequence groups. Further, the sequence groups were comparable with respect to chemotherapy, prior chemotherapy, sex, and age.

The efficacy results are reported in terms of mean and standard deviation as a function of cycle 1, cycle 2, and both cycles. Striking group differences favoring nabilone are observed for frequency of vomits, severity of nausea, and global efficacy. Nabilone also causes more adverse effects than compazine.

Table 13:
Descriptive Statistics of Daily Averages and
Investigator's Global Impressions
(Table 2A, Sponsor's Analysis Vol 1.11, Appendix E, pg 171)

	Daily Averages			Investigator's Global Impressions	
	Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1					
Nabilone Mean	3.35	1.22	1.08	1.62	0.95
S.D.	3.98	0.83	0.78	0.74	0.59
n	21	21	21	21	21
Compazine Mean	10.06	1.99	0.79	3.00	0.40
S.D.	11.07	0.60	0.40	1.13	0.51
n	13	15	15	15	15
Cycle 2					
Nabilone Mean	3.06	1.39	0.87	1.67	1.13
S.D.	3.40	0.81	0.54	1.05	0.52
n	13	15	15	15	15
Compazine Mean	8.46	1.64	0.81	3.00	0.67
S.D.	10.51	1.00	0.67	1.18	0.66
n	21	21	21	21	21
Both Cycles					
Nabilone Mean	3.24	1.29	0.99	1.64	1.03
S.D.	3.72	0.82	0.69	0.87	0.56
n	34	36	36	36	36
Compazine Mean	9.08	1.78	0.80	3.00	0.56
S.D.	10.59	0.86	0.57	1.15	0.61
n	34	36	36	36	36

The results of the non-parametric analysis are shown in Table 14. There were no significant residual or cycle effects noted. Treatment effects favoring nabilone were observed for frequency of vomiting (day 1 $p = .004$; total average $p < .001$), severity of nausea (day 1 $p = .058$, total average $p = .004$) and food intake (total average $p = .04$). However, nabilone had a higher incidence of adverse effects ($p = .004$).

Table 14:
 Non-Parametric Crossover Analysis
 on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.11, Appendix E, pg 173)

	Mean Ranks		Z-value	P-value
	Seq. Gp. 1 (n=21)	Seq. Gp. 2 (n=15)		
Residual Effects				
Freq. of Vomits - Average	16.69	21.03	1.24	.217
- Day 1	16.40	21.43	1.43	.153
Sev. of Nausea - Average	16.71	21.00	1.22	.223
- Day 1	17.19	20.33	0.90	.369
Food Intake - Average	18.71	18.20	-0.13	.500
- Day 1	19.71	16.80	-0.80	.422
Efficacy	18.24	18.87	0.19	.500
Adverse Effects	19.45	17.17	-0.63	.500
Treatment Effect				
	(N-C)*	(C-N)*		
Freq. of Vomits - Average	13.55	25.43	3.35	<.001
- Day 1	14.29	24.40	2.86	.004
Sev. of Nausea - Average	14.21	24.50	2.90	.004
- Day 1	15.71	22.40	1.89	.058
Food Intake - Average	21.57	14.20	-2.05	.040
- Day 1	20.50	15.70	-1.33	.183
Efficacy	12.43	27.00	4.11	.001
Adverse Effects	22.81	12.47	-2.89	.004
Cycle Effect				
Freq. of Vomits - Average	19.79	16.70	-0.85	.395
- Day 1	20.12	16.23	-1.07	.282
Sev. of Nausea - Average	19.52	17.07	-0.67	.500
- Day 1	20.64	15.50	-1.43	.153
Food Intake - Average	20.52	15.67	-1.35	.178
- Day 1	19.79	16.70	-0.85	.395
Efficacy	18.86	18.00	-0.22	.500
Adverse Effects	16.33	21.53	1.48	.140

*N-Nabilone, C-Compazine

The categorical analysis of the crossover data as presented in Tables 14A and 14B. In general, the analyses support the results obtained in the non-parametric analysis of the ranked data. However, the categorical analysis appears less robust.

Table 14A
Crossover Frequency Analysis
(Table 6A, Sponsor's Analysis, Vol 1.11, Appendix E, pg 175)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u>	<u>Seq.</u>	<u>Total</u>	<u>Cycle</u>	<u>Treatment</u>
	<u>Gp. 1</u>	<u>Gp. 2</u>			
	<u>(n=21)</u>	<u>(n=15)</u>	<u>(n=36)</u>		
Frequency of vomits - Average					
Nabilone Better	16	11	27	.500	.004
Same	1	0	1		
Compazine Better	4	4	8		
Frequency of vomits - Day 1					
Nabilone Better	10	11	21	.500	.099
Same	5	0	5		
Compazine Better	6	4	10		
Severity of Nausea - Average					
Nabilone Better	12	9	21	.500	.005
Same	6	4	10		
Compazine Better	3	2	5		
Severity of Nausea - Day 1					
Nabilone Better	4	7	11	.282	.282
Same	13	7	20		
Compazine Better	4	1	5		
Food Intake - Average					
Nabilone Better	13	5	18	.500	.150
Same	4	7	11		
Compazine Better	4	3	7		
Food Intake - Day 1					
Nabilone	17	2	9	.500	.473
Same	12	12	24		
Compazine Better	2	1	3		

The data in Table 14B corroborate the investigator's impressions in Table 13 that nabilone is more efficacious but has a higher incidence of side effects. Of particular interest, however, is the patient preference data. Patients clearly favored nabilone (29 to 6, $p < .001$)

Table 14B
Crossover Frequency Analysis
(Table 6B, Sponsor's Analysis, Vol 1.11, Appendix E, pg 176)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq. Gp. 1 (n=21)</u>	<u>Seq. Gp. 2 (n=15)</u>	<u>Total (n=36)</u>	<u>Cycle Effect</u>	<u>Treatment Effect</u>
Clinical Global Impressions					
Efficacy					
Nabilone Better	15	11	26	.413	<.001
Same	6	2	8		
Compazine Better	0	2	8		
Clinical Global Impressions					
Adverse Effects					
Nabilone Better	3	1	4	.500	.013
Same	11	4	15		
Compazine Better	7	10	17		
Patient's Preference					
Nabilone Better	17	12	29	.500	<.001
Same	0	1	1		
Compazine Better	4	2	6		

Table 15 is a summary of frequency data as a function of chemotherapy group. It is obvious that nabilone is at least as effective in the cisplatin regimens as the noncisplatin regimens. Patients in the cisplatin group preferred nabilone over compazine (18 to 5).

Table 15 (Tables 7A & 8, Sponsor's Analysis, Vol 1.11, Appendix E, pg 177-78)
 Frequency of Patients by Chemotherapy Groups

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=23)</u>	<u>Other than Cis-Platinum (n=13)</u>	<u>Total</u>
Freq. of Vomits - Average			
Nabilone Better	19	8	27
Same	1	0	1
Compazine Better	3	5	8
Freq. of Vomits - Day 1			
Nabilone Better	14	7	21
Same	4	1	5
Compazine Better	5	5	10
Severity of Nausea - Average			
Nabilone Better	15	6	21
Same	7	3	10
Compazine Better	1	4	5
Severity of Nausea - Day 1			
Nabilone Better	6	5	11
Same	16	4	20
Compazine Better	1	4	5
Food Intake - Average			
Nabilone Better	12	6	18
Same	7	4	11
Compazine Better	4	3	7
Food Intake - Day 1			
Nabilone Better	3	6	9
Same	20	4	24
Compazine Better	0	3	3
Clinical Global Impressions			
Efficacy			
Nabilone Better	16	10	26
Same	7	1	8
Compazine Better	0	2	2

Table 15 (Cont'd)

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=23)</u>	<u>Other than Cis-Platinum (n=13)</u>	<u>Total</u>
Clinical Global Impressions			
Adverse Effects			
Nabilone Better	2	2	4
Same	10	5	15
Compazine Better	11	6	17
Patient's Preference			
Nabilone Better	18	11	29
Same	0	1	1
Compazine Better	5	1	6

The sponsor also analyzed efficacy and safety data from all patients enrolled in cycle 1 (Table 16). Significant differences favoring nabilone were obtained with respect to day 1 vomits ($p = .002$), average daily vomits ($p = .008$), day 1 nausea severity ($p = .043$) and average daily nausea ($p = .005$). Investigator rated efficacy also favored nabilone ($p = .001$). In the cycle 1 patients, the investigators also rated nabilone as producing more severe side effects ($p = .009$). However, the rating equaled the "did not significantly interfere with patient's functioning" level.

Comments:

This investigation has demonstrated superior antiemetic and antinausea activity of nabilone compared to compazine. The rank analysis and the categorical analysis of the evaluable patients are corroborated by the all patients analysis of cycle 1. Thus, there is no apparent bias introduction into the analysis by the dropouts.

The patient preference data infer the patients favorably perceive nabilone. This is an indication that the high incidence of side effects are not considered to be overly distressing or intolerable to the majority of patients. This is an important point as most of the commonly reported side effects are of the central nervous system variety (e.g., mood changes (anxiety, depression, elation, giddiness), a "high", somnolence, vertigo, headache and blurred vision.)

One issue related to the last point is whether the nature of the side effects could have disrupted the blind for both patients and

investigators. I believe that the blind was broken for the investigator(s) if not the patients. This leads one to the question of whether or not the study is fatally flawed as a result of the blind being broken. I think not in this instance. I find the most impressive data to be the vomiting frequency. Although some expectation effect may account for a portion of the observed difference, I find it difficult to believe that expectation could have played anything but a minor role in the response. Thus, the study can be considered adequate and well-controlled, supporting the claim of an antiemetic effect of nabilone.

In the Indications section of the labeling, it would be appropriate to identify the major treatment group and the regimen. i.e., testicular cancer patients receiving cisplatin (20 mg/M²), vinblastine and bleomycin. The significance of this point is two-fold: (1) it identifies a patient population in which nabilone's efficacy was demonstrated; and (2) the combination chemotherapy of nonseminomatous testicular cancer (developed by) appears to induce significant (@ 90%) regressions and a fairly high cure rate. Thus, nabilone would be recommended for use in one of the most successful chemotherapy regimens.

Table 16 (Table 8, Sponsor's Analysis, Vol 1.11, Appendix E, p. 179)
Cycle 1 - All Patients

	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
	Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone								
Mean	3.46	6.35	1.26	1.59	1.10	1.15	1.76	1.00
S.D.	3.93	10.27	0.85	0.97	0.78	0.82	0.88	0.58
n	26	26	27	27	27	27	25	25
Median (n=27)	3.00	3.00	1.20	2.00	1.00	1.00	2.00*	1.00*
Compazine								
Mean	8.57	12.28	1.92	2.20	0.81	0.95	2.95	0.45
S.D.	9.66	9.22	0.54	0.52	0.37	0.60	1.05	0.51
n	18	18	20	20	20	20	20	20
Median (n=20)	6.70	11.00	2.00	2.00	1.00	1.00	3.00	0.00

Non-Parametric Analysis

Mean Rank	Nabilone		Compazine		Z-value		P-value	
Nabilone	19.48	18.57	30.10	31.32	2.64	3.16	.008	.002
Compazine	19.13	20.54	30.57	28.67	2.84	2.02	.005	.043
	25.50	25.11	21.97	22.50	-0.86	-0.63	.389	.500
	16.90	27.62	30.63	17.22	3.49	-2.63	.001	.009

*n=25

Investigator 306

This study enrolled male and female, in- and outpatients between the ages of 23 and 78. Ten (10) patients, 4 male and female were enrolled. The study was suspended in January, 1979 due to toxicity data obtained in the one-year toxicity study in the dog. At that time, 7 evaluable patients had entered the trial.

Three patients had breast cancer and 2 had a diagnosis of lymphoma. The other 5 patients each had a different type of cancer.

Five (5) of the 10 patients received concomitant medications. The two lymphoma patients were treated with prednisone as a concomitant medication.

The evaluable patients are summarized below in Table 17 (Table 2, Sponsor's Analysis, Vol 1.11, Pg 210).

Table 17: Cancer chemotherapy - Evaluable Patients

<u>Regimen</u>	<u>Cancer</u>	<u>Frequency</u>
Adriamycin, cyclophosphamide	Breast	2
Adriamycin, dacarbazine	Connective and mesothelioma	2
Adriamycin, cyclophosphamide vincristine	Lymphoma	2
Adriamycin, mitomycin, 5-fluorouracil	Adenocarcinoma	<u>1</u>
Total		7

The results were not subjected to statistical analysis. The median number of vomits was 10 and 15 for nabilone and compazine, respectively. Average nausea ratings were 1.29 for nabilone and 1.71 for compazine. Six (6) of the 7 evaluable patients preferred nabilone.

(5) Composite analysis

Of the 126 patients entered, 75 (60%) were considered evaluable. Investigator 301 (Young) found few differences between nabilone and compazine, investigator 302 found nabilone superior to compazine with respect to emesis and nausea, and investigator 306 had a small sample size (7 patients) that had a trend towards nabilone superiority. One of the interesting aspects of this multicentered trial is the heterogeneity of cancer types and associated variables. This is

reflected in the statistical analysis which found statistically significant differences for chemotherapy, prior chemotherapy, sex, age and an investigator by evaluability interaction (the proportion of evaluable patients was different across the three investigators). In a very real sense, the only significant issue in the composite analysis is whether the negative results of investigator 301 will counter the positive results favoring nabilone found by investigator 302, causing a loss of power and/or investigator or investigator by treatment interactions.

The combined results obtained on the efficacy variables are displayed in Table 18. The frequency of vomiting data is shown both with and without the contribution of investigator 306. There are obvious trends towards reduced nausea and vomiting with nabilone. The overall means generated by the three investigators infer that nabilone may be more efficacious with less side effects.

Table 18 (Table 3C, Sponsor's Analysis, Vol 1.10, Appendix C, pg 78)

Means
Both Cycles Combined

Drug	Investigator	n	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
			Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone	301	32	7.85a	7.85a	1.38	1.38	1.16	1.16	2.31	0.94
	302	32	3.24b	6.47b	1.29	1.58	0.99	1.06	1.64	1.03
	306	7	7.00c	7.00c	1.29	1.29	0.86	0.86	2.14	1.00
Composite		75	5.43d	7.07d	1.33	1.47	1.05	1.08	1.97	0.99
		(68)	(5.28)e (7.08)e							
Compazine	301	32	7.96a	7.96a	1.72	1.72	1.00	1.00	3.22	0.50
	302	36	9.08b	12.59b	1.78	1.94	0.80	0.86	3.00	0.56
	306	7	20.33c	20.33c	1.71	1.71	0.71	0.71	3.14	0.57
Composite		75	9.64d	11.42d	1.75	2.83	0.88	0.91	3.11	0.53

n=27, b_n=34, c_n=6. d_n=67. e_n=61

() = without investigator 306

The results of the composite crossover analysis of variance on the ranked data. When corrected for an investigator by residual interaction which resulted in dropping the frequency of vomiting data from investigator 306, and corrected for an investigator by treatment interaction (by determination of a new error mean square term using the appropriate investigator by treatment sum of squares), significant differences favoring nabilone were evident with respect to all subject-rated efficacy variables. The investigator-rated variables showed a difference in adverse event severity, favoring compazine.

Table 19:
Crossover Analysis of Variance on Ranks
(Table 5, Sponsor's Analysis, Vol 1.10, Appendix C, pg 82)

Treatment Effect	Investigator		Residual		Inv. x Residual		Error	
	S.S.a	P	S.S.b	P	S.S.a	P	S.S.c	S.S.c
Freq. of Vomits - Average	1436	.215	1182	.112	2625	.063	31518	
- Day 1	610	.500	1034	.141	2904	.050	32096	
Sev. of Nausea - Average	182	.500	460	.330	1518	.211	32899	
- Day 1	791	.418	309	.409	1046	.316	30850	
Food Intake - Average	1408	.228	197	.500	725	.463	32124	
- Day 1	996	.332	73	.500	751	.434	30678	
Efficacy	3029	.035	1394	.076	1207	.253	29718	
Adverse Effects	608	.497	201	.497	802	.399	29694	
Removing INV = 306								
Freq. of Vomits - Average	657b	.198	42	.500	563b	.233	24811d	
- Day 1	54b	.500	142	.500	601b	.222	25333d	
Treatment Effect	Investigator		Treatment		Inv. x Treatment		Error	
	S.S.a	P	S.S.b	P	S.S.a	P	S.S.c	S.S.c
Freq. of Vomits*- Average	30b	.500	2590	.007	1620	.032	21643	
- Day 1	211b	.444	1834	.027	1182b	.073	22777	
Sev. of Nausea - Average	233	.500	2774	.007	305	.500	24770	
- Day 1	617	.425	1907	.024	9	.500	24544	
Food Intake - Average	980	.314	2764	.012	596	.493	28714	
- Day 1	902	.299	2141	.018	458	.500	25287	
Efficacy	241	.500	5083	.001	287	.500	23323	
Adverse Effects	1090	.235	3448	.003	193	.500	25439	

a d.f.=2, b d.f.=1, c d.f.=6; d d.f.=64

*Omitting Investigator 306

Analysis of all cycle 1 patients showed an investigator effect and significant (day 1) and nearly significant (p<0.10) investigator by treatment effects for day 1 and average frequency of vomiting, respectively. I believe the statistical analysis of the cycle 1 group is showing that the results across investigators are not comparable on the frequency of vomiting data. Further, cycle 1 data are insensitive to treatment differences.

Table 20:
 Cycle 1 - All Patients
 Analysis of Variance on the Ranks
 (Table 8, Sponsor's Analysis, Vol 1.10, Appendix C, pg 86)

Treatment Effect	Investigator		Treatment		Inv. x Treatment		Error S.S.C	d.f.
	S.S.a	P	S.S.b	P	S.S.a	P		
Freq. of Vomits- Average	7747	.020	8	.500	4457	.102	101242	106
- Day 1	1958	.374	106	.500	6260	.046	104444	106
Sev. of Nausea - Average	2913	.214	366	.500	3573	.152	97880	105
- Day 1	197	.500	167	.500	2869	.204	93370	105
Food Intake - Average	96	.500	51	.500	472	.500	93099	103
- Day 1	540	.500	9	.500	485	.500	85287	103
Efficacy	3975	.088	3244	.047	2170	.262	81528	102
Adverse Effects	508	.500	7284	.002	387	.500	74065	102

ad.f.=2, bd.f.=1

The analysis of patient preference showed that for both evaluable patients (evaluable plus unevaluable) showed that patients in both groups preferred nabilone ($p < .001$), both groups.

Conclusions:

The results obtained in this study demonstrate the antiemetic superiority of nabilone over compazine in patients receiving cancer chemotherapy. The effect was most notable in the study (#302) in which a fairly homogenous group of patients was studied. The labeling should identify that nabilone is effective against nausea and vomiting produced by cisplatin (20 mg/m²), vinblastine and bleomycin in testicular cancer patients.

In the discussion of the data, I noted that I believed the blind could not have been maintained but that this was not a serious flaw in judging the results. My comments are also applicable to the overall conclusions inasmuch as the data are the major component of the data demonstrating nabilone's antiemetic superiority over compazine.

b. Protocol #7

Investigator

This study was conducted in cancer patients from the

This was a double-blind, randomized crossover study comparing the safety and efficacy of nabilone versus compazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents in two consecutive chemotherapy cycles. Patients were randomly assigned to receive either nabilone or prochlorperazine during the first cycle of chemotherapy and the other drug during the second cycle. The study drug was to be administered throughout the chemotherapy cycle, a 1 to 5-day treatment period. Chemotherapy cycles were usually given 3 to 6 weeks apart.

Administration of the test drug began the evening before chemotherapy. Dosing was continued 1/2 hour before chemotherapy and 1/2 hour before meals throughout the course of chemotherapy. Dosing with nabilone varied and ranged from 1 to 6 mg/day. Compazine doses ranged from 10 to 30 mg per day.

Criteria for study participation were that cancer patients, aged 17 to 70, of either sex could participate. These patients had to have experienced severe nausea and vomiting with previous courses of chemotherapy. Pregnant women and patients with severe atherosclerotic vascular disease were ineligible.

Efficacy was determined by three patient-related criteria every 24 hours of chemotherapy. The criteria were the frequency of vomiting, the severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual amount, more than usual). In addition to the sponsor's analysis, the investigator performed an apparent post-hoc analysis on the quality of the antiemetic response in evaluable subjects. Responses were scored as complete if no nausea or vomiting were recorded, partial if a 50% or greater reduction in nausea and vomiting was achieved, and "no response" if a less than 50% reduction in nausea and vomiting were recorded.

Safety evaluation included a medical history, hematology, and SMA 12/60 completed on each patient prior to each period of study drug. The test battery was repeated prior to the next chemotherapy and following each patient's termination. Adverse reactions were recorded by patients; investigator(s) recorded on a separate report from his/their evaluation of adverse experiences and his/their opinion as to the relationship to study drug.

The primary diagnosis for the study was nausea and vomiting associated with cancer chemotherapy. Secondary diagnosis was any type of cancer being treated by a chemotherapeutic agent(s) known to cause nausea and vomiting. Each patient's age, sex, intercurrent illnesses and concomitant medications were also recorded.

Patients were considered evaluable if they completed at least one day on each study drug and no "protocol violations" occurred on these days in either cycle. The lesser of the two numbers; i.e., evaluable days in cycle 1 versus evaluable days in cycle 2, was used in the analysis.

Efficacy parameters were considered independently when assigning evaluability; i.e., missing data from one parameter did not negate an evaluation of the other parameters.

Protocol violations were defined as any event listed below:

- (1) A second antiemetic was given other than the study drug assigned by the randomization schedule;
- (2) Study drug was not administered concomitantly with chemotherapy;
- (3) Specific dose of antiemetic, as called for by the study protocol, was not given 30 minutes prior to chemotherapy;
- (4) A different chemotherapy regimen was instituted in the second chemotherapy cycle; and
- (5) Smoking marijuana on either cycle.

Statistical Analysis

The sequence groups were analyzed with respect to evaluability, chemotherapy, prior chemotherapy, sex and age and interaction effects (group x sex x evaluability).

The data analysis was essentially that described in protocol 20. A non-parametric analysis of ranks was performed. Data were analyzed for residual effects before both cycles were combined. Categorical analysis was performed on the variables (nabilone better, same, compazine better) with respect to cycle and treatment effects. An analysis of all patients in cycle 1 was performed.

Blood pressure changes (recumbent and standing) were analyzed for direction of change within drug therapy and magnitude of change across therapy.

Patient characteristics

Forty-three (43) patients enrolled in the study; 18 were male and 25 female. Twenty-nine (29) patients aged 17 to 70 were considered evaluable for the efficacy analysis. The type of cancers found in the population are listed below in Table 21.

Table 21:
Frequency of Cancer Type in Study Population

<u>Type</u>	<u>Number</u>	<u>(%)</u>
Hodgkin's	13	(30)
Non-Hodgkin's lymphoma	8	(19)
Breast	8	(19)
Other*	14	(32)

*These occurred with a frequency of 3 or less

The most frequent treatment used was bleomycin, nitrogen mustard, procarbazine and vincristine in patients with Hodgkin's disease. The chemotherapy by evaluability and sequence groups is given in Table 22.

Table 22
Cancer Chemotherapy By Evaluability and Sequence Group
(Table 1, Sponsor's Analysis, Vol. 1.15, pg 13)

<u>Cancer Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>
Cisplatin + other chemotherapies	3	1	4	2	0	2
Adriamycin + other chemotherapies*	5	6	11	3	3	6
Other than cisplatin or Adriamycin	<u>3</u>	<u>11</u>	<u>14</u>	<u>5</u>	<u>1</u>	<u>6</u>
Total	11	18	29	10	4	14

*Not including cisplatin

As can be seen by inspection, the statistical analysis verified a group by evaluability interaction. Further, the sequence by chemotherapy by evaluability interaction was statistically significant ($p = .031$).

The mean and standard deviations of the efficacy parameters (day 1 and average) are displayed as individual cycle data and combined data in Table 23. Further, the standard deviations are approximately equal to the means. This indicates a high degree of variability in the antiemetic response to both drugs. There is also an indication of a cycle effect as vomiting in both treatment groups appears more frequent in the second cycle.

Table 23:
Descriptive Statistics
Daily Averages

(Table 2, Sponsor's Analysis, Vol 1.15, Appendix E, pg 147)

		Daily Averages					
		Freq. of Vomits		Severity of Nausea		Food Intake-	
		Average	Day 1	Average	Day 1	Average	Day 1
Cycle 1							
Nabilone	Mean	4.70	4.90	1.41	1.73	1.07	1.00
	S.D.	5.38	5.30	1.11	1.27	0.71	0.77
	n	10	10	11	11	11	11
Compazine	Mean	7.57	8.24	1.71	1.83	1.08	1.06
	S.D.	11.13	11.15	1.21	1.34	0.75	0.73
	n	17	17	18	18	18	18
Cycle 2							
Nabilone	Mean	5.88	7.35	1.52	1.78	1.19	1.11
	S.D.	7.22	7.77	1.19	1.31	0.55	0.68
	n	17	17	18	18	18	18
Compazine	Mean	11.70	13.10	1.82	2.18	0.80	0.55
	S.D.	9.71	11.00	1.05	1.08	0.53	0.52
	n	10	10	11	11	11	11
Both cycles							
Nabilone	Mean	5.44	6.44	1.48	1.76	1.15	1.07
	S.D.	6.51	6.95	1.15	1.27	0.60	0.70
	n	27	27	29	29	29	29
Compazine	Mean	9.10	10.04	1.75	1.97	0.97	0.86
	S.D.	10.63	11.14	1.13	1.24	0.68	0.59
	n	27	27	29	29	27	27

The results of the non-parametric crossover analysis are displayed in Table 24. There is a trend towards antiemetic superiority ($p = .10$) with nabilone. The differences between the two drugs are not as great as the difference in vomiting between cycles. Day 1 vomits were significantly different ($p = .031$) with respect to cycle whereas average vomits were marginally ($p = .058$) different between cycles. There was no residual effect observed on any of the three efficacy parameters.

Table 24:
 Non-Parametric Crossover Analysis on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.15, Appendix E, pg 149)

	Seq. Gp. 1		Seq. Gp. 2		Z-value	P-value
	n	Mean Rank	n	Mean Rank		
Residual Effects						
Freq. of Vomits- Average	10	14.40	18	14.56	-0.02	.500
- Day 1	10	14.10	18	14.72	-0.17	.500
Sev. of Nausea - Average	11	14.82	18	15.11	0.07	.500
- Day 1	11	15.59	18	14.64	0.31	.500
Food Intake - Average	11	13.64	18	15.83	-0.65	.500
- Day 1	11	12.27	18	16.67	-1.33	.185
Treatment Effect						
		(N-C)*		(C-N)*		
Freq. of Vomits- Average	10	11.10	18	16.39	-1.61	.108
- Day 1	10	11.45	18	16.90	1.44	.150
Sev. of Nausea - Average	11	12.23	18	16.69	1.35	.178
- Day 1	11	12.73	18	16.39	1.10	.271
Food Intake - Average	11	17.82	18	13.28	1.42	.157
- Day 1	11	18.05	18	13.14	1.53	.127
Cycle Effect						
Freq. of Vomits- Average	10	10.50	18	16.72	-1.89	.058
- Day 1	10	9.95	18	17.03	-2.16	.031
Sev. of Nausea - Average	11	15.09	18	14.94	0.07	.500
- Day 1	11	13.82	18	15.72	-0.56	.500
Food Intake Average	11	15.55	18	14.67	0.29	.500
- Day 1	11	16.95	18	13.81	0.99	.323

*N=Nabilone, C=Compazine

The crossover frequency analysis (Table 25) showed trends toward cycle effects for day 1 vomits (p = .119) and average vomits (p = .193). No statistically significant differences between nabilone and compazine were found in the analysis. Thus, using this type of analysis, no superiority of nabilone over compazine was demonstrated.

Table 25:
Crossover Frequency Analysis
(Table 4, Sponsor's Analysis, Vol 1.10, Appendix E, pg 281)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits - Average					
Nabilone Better	6	8	14	.193	.297
Same	3	1	4		
Compazine Better	<u>1</u>	<u>9</u>	<u>10</u>		
Total	10	18	28		
Freq. of vomits - Day 1					
Nabilone Better	6	7	13	.119	.436
Same	3	1	4		
Compazine Better	<u>1</u>	<u>10</u>	<u>11</u>		
Total	10	18	28		
Severity of Nausea - Average					
Nabilone Better	5	8	13		
Same	3	6	9	.500	.413
Compazine Better	<u>3</u>	<u>4</u>	<u>7</u>		
Total	11	18	29		
Severity of Nausea - Day 1					
Nabilone Better	5	5	10	.500	.500
Same	4	9	13		
Compazine Better	<u>2</u>	<u>4</u>	<u>6</u>		
Total	11	18	29		
Food Intake - Average					
Nabilone Better	4	8	12	.500	.402
Same	5	6	11		
Compazine Better	<u>2</u>	<u>4</u>	<u>6</u>		
Total	11	18	29		
Food Intake - Day 1					
Nabilone Better	5	6	11	.500	.500
Same	5	8	13		
Compazine Better	<u>1</u>	<u>4</u>	<u>5</u>		
Total	11	18	29		

The cycle 1 analysis of all patients failed to show any statistically significant differences between nabilone and compazine on any of the efficacy parameters (data not shown). Thus, on these measures, antiemetic

superiority was not demonstrated. However, the investigators performed a post-hoc analysis on the quality of the antiemetic response. The results of this study are displayed in Table 26 (Table 14), Sponsor's Analysis, Vol. 1.15, pg 28).

Table 26:
Quality of Antiemetic Response in 33 Evaluable Patients

<u>Drug</u>	<u>Response</u>		
	<u>Complete</u>	<u>Partial</u>	<u>None</u>
Nabilone	9 (27%)	21 (64%)	3 (5%)
Compazine	0	11 (33%)	22 (56%)

The investigators applied a sign test to test the association of drug with response. They also compiled vomiting data (61 + risk days) which they evaluated by the sign test. The results of combined complete and partial responses clearly favor nabilone ($p < .001$). The results of the complete response category also favor nabilone ($p < .005$). The results of the sign test showed a statistically significant reduction in the number of days with greater vomiting frequency ($p = 0.05$, sign test).

Comment:

Although these data are a very interesting analysis, there may be a bias involved due to dropouts (8/13 dropouts were due to intolerable or unacceptable side effects due to nabilone) or scoring criteria (several of the partial responses to compazine were nearly complete). At any rate, we were not supplied with baseline (previous) vomiting data. Thus, it is not possible to recalculate the results or perform other non-parametric analyses of the data. The problem with accepting the results of the sign test is that a bias may have occurred due to the 8 dropouts.

Conclusion:

The results of this study suggest a trend toward antiemetic superiority of nabilone over compazine. However, as statistically significant superiority was not demonstrated, this study does not support the efficacy of nabilone.

c. Protocol #9

Investigator

This study was conducted in cancer patients:

. This study was a double-blind, randomized crossover study comparing the safety and effectiveness of nabilone versus compazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents

in two consecutive chemotherapy cycles. Patients were randomly assigned to receive either nabilone or compazine during the first cycle and the 4 other drugs during the second cycle. The study drug was administered concomitant with chemotherapy throughout the 1- to 5-day chemotherapy cycle. Chemotherapy cycles were usually 2 to 4 weeks apart.

Administration of the test drug to the first 60 patients began 30 minutes before chemotherapy. The protocol was amended to allow dosing to begin the evening before chemotherapy. Nabilone was administered as a 1 mg capsule and compazine was administered as a 5 mg capsule. The schedule of administration was 2 mg nabilone, q. 6h., p.r.n., or 10 mg compazine, q. 6h., p.r.n. Capsules were identical in appearance to maintain the double-blind nature of the study.

Criteria for participation were that patients had to be receiving chemotherapy known to cause nausea and vomiting. Informed consent was obtained from each patient. Pregnant women and patients with cardiac disease were excluded from the protocol.

Efficacy was determined on the patient-rated variables per 24-hour period of chemotherapy. Patients recorded the number of vomiting episodes, the severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual amount, more than usual).

Safety data included a history and physical examination prior to each course of chemotherapy. Laboratory testing included hematology and blood chemistry (SMA 12/60) before and after each cycle. Blood pressure and heart rates were obtained in patients after lying, sitting and standing. Determinations were performed every 6 hours following study drug administration and for 12 hours after study completion. Adverse reactions were noted by patients and the investigators. The investigator rendered an opinion as to the cause of the reaction.

The primary diagnosis of the patients was nausea and vomiting due to cancer chemotherapy. The secondary diagnosis was the type of cancer being treated by cancer chemotherapeutic agents known to cause nausea and vomiting. Each patient's sex, age, intercurrent illnesses and concomitant medications were also recorded.

Patients were considered evaluable if they completed at least one day of study drug administration on each cycle. The total number of evaluable days per cycle were the number of consecutive days of test drug administration in which no protocol violations occurred. The lesser of the two numbers of evaluable days per cycle was used in the efficacy analysis.

Efficacy parameters were considered independently when considering evaluability of data.

Protocol violations were the same as those used in Protocol 7, and are listed below:

- (1) A second antiemetic was given other than the study drug assigned by the randomization schedule;
- (2) Study drug was not administered concomitantly with chemotherapy;
- (3) Specific dose of antiemetic, as called for by the study protocol, was not given 30 minutes prior to chemotherapy;
- (4) A different chemotherapy regimen was instituted in the second chemotherapy cycle; and
- (5) Smoking marijuana on either cycle.

Statistical Analysis

The sequence groups were analyzed with respect to evaluability, cancer diagnosis, chemotherapy, prior chemotherapy, sex, age and interaction effects.

Data analysis was essentially that described in Protocol 20. A non-parametric analysis of ranks was performed for each cycle and both cycles combined (after testing for a residual effect and finding none). The crossover frequency analysis compared the treatment and tested for cycle effects. Further, an analysis of all patients in cycle 1 was performed.

Blood pressure changes were analyzed for statistical significance for direction of change within drug therapy and magnitude of change across drugs.

Patient Characteristics

Ninety-eight (98) patients (83 male, 15 female) aged 15 to 74 were enrolled in the trial. Eighty-three (83) patients completed the crossover. The type of cancers found in the study population are listed below in Table 27.

Table 27:
Frequency of Cancer Type By Cycle in Protocol 9

<u>Type</u>	<u>Number</u>	<u>(%)</u>	<u>Cycle 1 evaluable</u>	<u>Cycle 2 evaluable</u>
Testicular	76 (78)		33	35
Ovarian	5	(5)	1	2
Bladder	5	(4)	1	2
Hodgkin's	4	(4)	0	2
Other	9	(9)	4	3

The most frequent chemotherapy regimen was 5 days of cisplatin (20 mg/M²) 1 or 2 days of bleomycin, vinblastine or adriamycin in the treatment of testicular cancer. Sixty-eight (68) of 83 completers had testicular cancer. Thus, the result will mostly reflect what happened in this population. The statistical analysis of patient and cancer treatment variables bears this out; i.e., the sequence (cycle) groups were comparable with respect to chemotherapy, previous chemotherapy, sex and age.

Fifteen (15) patients failed to complete the crossover. Of these, 8 patients were terminated early according to Table 28. Further, 7 patients (#12, 18, 26, 36, 58, 67, and 91) were considered unevaluable due to protocol violations. Patient #44 terminated after 1 dose of nabilone in cycle 2 but was counted in the efficacy analysis.

Table 28: Reasons for Early Terminations
(Table 10, Sponsor's Analysis, Vol. 1.14, pg 25)

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse experience (nabilone)	4	11, 14, 15, 44
Lack of efficacy (nabilone)	1	29
Lack of efficacy (nabilone and prochlorperazine)	2	65
Physician decision	2	5, 27
Complicating decisions	1	1

The tabulation of patient doses of test drug by day of chemotherapy is given in Table 29. Sixty-eight (68) of 94 (72%) of those receiving nabilone on day 1 continued with nabilone on day 5. Seventy (70) of 91 (77%) of those receiving compazine on day 1 were still receiving it on day 5. In both treatment groups there is a shift towards lower dosage on days 3 through 5 of the chemotherapy cycle.

Table 29 (Table 11, Sponsor's Analysis, Vol. 1.14, pg 28)
 Frequency of Patients by Total Daily Dose
 Inv. 201

	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Nabilone							
1 or 2 mg	25	21	18	24	27	27	
3 or 4 mg	8	30	28	20	19	14	
Greater than 4 mg	2	43	38	33	28	27	
Total	35	94	84	77	74	68	
Prochlorperazine							
1 or 2 mg	20	19	18	25	25	31	
15 or 20 mg	9	35	22	15	14	14	
25 or 30 mg	0	12	20	15	12	14	
Greater than 30 mg	2	25	25	23	25	11	
Total	31	91	85	78	76	70	

Efficacy data are tabulated in terms of means and standard deviations in Table 30. Visual inspection of the data suggest both treatment and cycle-related effects for the 3 parameters. Combined means from both cycles suggest a superior antiemetic effect for nabilone.

Table 30:
Descriptive Statistics
Daily Averages
(Table 2, Sponsor's Analysis, Vol 1.14, Appendix E, pg 371)

		Daily Averages					
		Freq. of Vomits		Severity of Nausea		Food Intake	
		Average	Day 1	Average	Day 1	Average	Day 1
Cycle 1							
Nabilone	Mean	1.96	5.23	1.29	1.82	1.20	1.21
	S.D.	1.80	5.65	0.89	1.19	0.57	0.66
	n	39	39	39	39	38	38
Compazine	Mean	6.50	9.79	1.70	2.12	0.85	0.86
	S.D.	7.62	8.76	0.90	0.99	0.52	0.68
	n	42	42	42	42	43	43
Cycle 2							
Nabilone	Mean	5.59	9.55	1.43	2.24	0.95	0.91
	S.D.	7.65	8.06	0.95	0.82	0.59	0.75
	n	42	42	42	42	43	43
Compazine	Mean	6.93	11.46	2.07	2.51	0.83	0.97
	S.D.	6.11	8.50	0.86	0.85	0.51	0.64
	n	39	39	39	39	38	38
Both cycles							
Nabilone	Mean	3.84	7.47	1.36	2.04	1.06	1.05
	S.D.	5.90	7.29	0.92	1.03	0.59	0.72
	n	81	81	81	81	81	81
Compazine	Mean	6.71	10.59	1.88	2.31	0.84	0.91
	S.D.	6.89	8.63	0.90	0.94	0.52	0.66
	n	81	81	81	81	81	81

The non-parametric analysis of the ranked data is presented in Table 31. There were no residual effects noted on any of the efficacy parameters. There were treatment-related effects favoring nabilone for day 1 ($p < .001$) and average vomiting frequency ($p < .001$), nausea severity day 1 ($p = .074$) and average ($p < .001$), and average food intake ($p < .001$). Additionally statistically significant cycle effects were observed for day 1 ($p = .006$) and average vomiting frequency ($p = .004$), and severity of nausea day 1 ($p = .009$) and average ($p = .05$).

Table 31:
 Non-Parametric Crossover Analysis
 (Table 4, Sponsor's Analysis, Vol 1.14, Appendix E, pg 373)

	Seq. Gp. 1		Seq. Gp. 2		Z-value	P-value
	n	Mean Rank	n	Mean Rank		
Residual Effects						
Freq. of Vomits- Average	39	40.97	44	42.91	-0.36	.500
- Day 1	39	39.60	44	44.13	-0.85	.396
Sev. of Nausea - Average	39	43.42	42	38.76	0.89	.372
- Day 1	39	41.44	42	40.60	0.17	.500
Food Intake - Average	38	43.45	43	38.83	-0.88	.376
- Day 1	38	45.33	43	37.17	-1.56	.118
Treatment Effect						
		(N-C)*		(C-N)*		
Freq. of Vomits- Average	39	16.60	44	55.65	-5.47	<.001
- Day 1	39	32.27	44	50.63	3.46	<.001
Sev. of Nausea - Average	39	28.21	42	52.88	4.71	<.001
- Day 1	39	36.14	42	45.51	1.79	.074
Food Intake - Average	38	51.86	43	31.41	3.91	<.001
- Day 1	38	45.13	43	37.35	1.49	.136
Cycle Effect						
Freq. of Vomits- Average	39	33.82	44	49.25	-2.91	.004
- Day 1	39	34.27	44	48.85	-2.75	.006
Sev. of Nausea - Average	39	35.67	42	45.95	-1.96	.050
- Day 1	39	33.91	42	47.58	-2.61	.009
Food Intake Average	38	45.13	43	37.35	1.49	.136
- Day 1	38	43.05	43	39.19	0.74	.458

*N=Nabilone, C=Compazine

The results of the categorical analysis are listed in Table 32. Treatment effects favoring nabilone were observed on day 1 vomits (p = .002), average vomits (p <.001), average severity of nausea (p <.001) and average food intake (p <.001). Cycle effects were also noted for day 1 vomits (p = .002) average frequency of vomiting (p <.001) and severity of nausea (p = .034). These results corroborate the results of the non-parametric crossover analysis (Table 31).

Table 31:
Crossover Frequency Analysis
(Table 6: Sponsor's Analysis, Vol 1.14, Appendix E, pg 375)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits - Average					
Nabilone Better	37	25	62	<.001	<.001
Same	1	6	7		
Compazine Better	<u>1</u>	<u>13</u>	<u>14</u>		
Total	39	44	83		
Freq. of vomits - Day 1					
Nabilone Better	32	19	51	.002*	.002*
Same	2	6	8		
Compazine Better	<u>5</u>	<u>19</u>	<u>24</u>		
Total	39	44	83		
Severity of Nausea - Average					
Nabilone Better	30	22	52	.493	<.001*
Same	3	12	15		
Compazine Better	<u>6</u>	<u>8</u>	<u>14</u>		
Total	39	42	81		
Severity of Nausea - Day 1					
Nabilone Better	18	10	28	.034*	.208*
Same	16	19	35		
Compazine Better	<u>5</u>	<u>13</u>	<u>18</u>		
Total	39	42	81		
Food Intake - Average					
Nabilone Better	21	19	40	.500	<.001
Same	13	17	30		
Compazine Better	<u>4</u>	<u>7</u>	<u>11</u>		
Total	38	43	81		
Food Intake - Day 1					
Nabilone Better	12	12	24	.500*	.167*
Same	21	22	43		
Compazine Better	<u>5</u>	<u>9</u>	<u>14</u>		
Total	38	43	81		

*From corrected chi-square test

The results of the "all patients" analysis of the first chemotherapy cycle are presented in Table 33. Statistically significant differences, favoring nabilone, are observed with all three efficacy parameters. Specifically, day 1 and average vomiting frequency favor nabilone, $p = .038$ and $p = .005$, respectively, as does food intake (average, $p = .022$). Average nausea severity exhibited a trend towards significance ($p = .09$) which favored nabilone.

Table 33:
Descriptive Statistics and Test Results
Cycle 1 - All Patients
(Table 8, Sponsor's Analysis, Vol 1.14, Appendix E, pg 377)

		Freq. of Vomits		Severity of Nausea		Food Intake-	
		Average	Day 1	Average	Day 1	Average	Day 1
Nabilone	Mean	3.11	6.91	1.33	1.89	1.13	1.14
	S.D.	6.12	8.72	0.95	1.20	0.63	0.71
	n	44	44	44	44	43	43
	Median	1.90	4.50	1.37	2.00	1.00	1.00
Compazine	Mean	6.02	9.58	1.64	2.12	0.85	0.84
	S.D.	7.50	8.76	0.84	0.98	0.48	0.68
	n	43	43	43	43	44	44
	Median	4.00*	8.00*	1.60	2.00	1.00	1.00

Non-Parametric Analysis

Mean Rank							
Nabilone	37.14	39.24	39.47	42.18	50.24	48.76	
Compazine	52.69	50.63	48.64	45.86	37.90	39.35	
Z-value	-2.84	-2.08	1.70	0.68	2.28	1.74	
P-value	.005	.038	.090	.494	.022	.082	

*n = 45

Conclusions:

In this study, nabilone appears to be a superior antiemetic to prochlorperazine. As the majority of the patients (82%) were testicular cancer patients receiving cisplatin or adriamycin, this fact could be highlighted in the Indications section of the labeling.

There is one issue regarding replication which deserves some discussion. Usually one likes to see replication of drug effect by different investigators in the same or similar study population. Both "positive" studies favoring nabilone over compazine were performed by the same investigator in essentially the same (cancer type) population. Although this is less desirable than replication by different investigators, the replication of an antiemetic superiority over compazine against cisplatin combination regimes (a potent emetic stimulus) is strongly persuasive of antiemetic efficacy of nabilone.

d. Protocol 28

Background:

This was a multicentered, double-blind, randomized, placebo-controlled crossover study comparing the effects of nabilone versus placebo in the treatment of nausea and vomiting associated with cyclic cancer chemotherapy. Six investigators participated in the trial. The sponsor analyzed the results of the individual investigators as well as the composite results. At the time of the NDA submission, three investigators [(#002 - , (#005 - and (#006 - had studies in progress. Data were analyzed from these studies on results obtained prior to NDA submission. To my knowledge, there were no subsequent amendments which supplied further data at study completion with reanalysis of all data.

Study design

This was a double-blind, randomized, placebo-controlled, two-period crossover study of the antiemetic effect of nabilone in cancer patients undergoing consecutive cycles of chemotherapy known to produce nausea and vomiting. Patients received nabilone or placebo during the first cycle of chemotherapy and were switched to the other drug treatment for the second cycle of chemotherapy. The study drug was administered concomitantly with chemotherapy, generally, a 1- to 5-day treatment course. Chemotherapy cycles were usually 3 to 6 weeks apart.

Study drug administration began the evening before chemotherapy. The study drug was to be administered 1 to 3 hours before initiation of chemotherapy and then once in the evening. The dose of nabilone for each administration was 2 mg. Placebo doses were administered in identical appearing capsules.

Criteria for study participation were that male or female, inpatients or outpatients had to be at least 16 years old, give written informed consent and be given a treatment regimen that was not expected to change over two consecutive chemotherapy courses. Eligible patients could be excluded on

the basis of any of the following factors: (1) receiving high dose cisplatin (100 mg/M²/day); (2) pregnancy; (3) no contraceptive use (fertile women); (4) clinically significant cardiovascular, hepatic, renal or CNS disease; (5) psychosis; (6) progressive disease of the eye(s); (7) weight of less than 45 kg; (8) alcohol or drug addiction; and (9) use of other psychotropic drugs, including marijuana, during the study.

Patients were to be randomized to a treatment group (nabilone or placebo) at time of admission. Assignment was stratified to insure a balanced distribution of patients who had previous chemotherapy and those who were beginning chemotherapy.

Efficacy criteria were rated by patients on a 24-hour basis. The patient-rated variables were vomiting frequency, severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual, more than usual). Patients were also asked to rate their preference for the antiemetic response in cycle 1 or cycle 2. Investigators rated global efficacy (very good, good, fair, poor, very poor) and adverse effects (none, did not interfere with patient's functioning, significantly interfered with patient's functioning, outweighed therapeutic effect).

Safety parameters included the taking of a medical history, physical examination at admission, and a physical examination after the study was completed. Clinical laboratory parameters (hematology - hemoglobin, hematocrit, reticulocyte, WBC, platelet count, and differential; SMA 12/60 and urinalysis) were determined within one week prior to cycle 1 and then within two weeks after study completion or discontinuation. Blood pressure and pulse rates were to be obtained within the week prior to each course of chemotherapy and after the second cycle had been completed or the study drug discontinued. Patients were to be monitored for postural hypotension 3 to 4 hours after the morning dose of study medication, where feasible. Recumbent and standing blood pressures were to be determined.

Adverse reactions volunteered by the patient or noted by an observer were to be recorded. The investigator was asked to rate the severity of the reaction as well as determine whether it was study drug-related.

To be considered evaluable for the crossover, patients had to complete at least one "evaluable" day on each cycle. Evaluable days were defined as the number of consecutive treatment days in which study drug and chemotherapy were administered and no "protocol violations" occurred. As in the other protocols, efficacy criteria were considered independently; i.e., missing data on one variable did not compromise the use of the data on other variables.

Three conditions were considered protocol violations:

1. administration of a second antiemetic, including marijuana, not assigned in the randomization schedule;
2. the specific dose of antiemetic was not administered 1-3 hours prior to chemotherapy; and
3. alteration of the chemotherapy regimen in cycle 2 of the protocol.

Statistical analysis

The sponsor analyzed several factors across investigators for comparability. The following analyses were performed with respect to sequence groups: cancer type, chemotherapy, previous chemotherapy, sex and age. In the individual analyses of each investigator, sequence groups (cycles) were compared with respect to evaluability, chemotherapy, previous chemotherapy, sex and age.

Efficacy data were tabulated with respect to mean and medians on the parameters. Individual and composite results are presented. The sponsor then performed a composite analysis incorporating both cycles using data from all investigators. Data were combined only after testing for a residual (carryover) effect. An analysis of variance was performed on the ranked data. A separate cycle analysis was also performed on the individual and composite data. Finally, a composite cycle 1 analysis on all patients was performed.

Blood pressure data were analyzed for the number of patients demonstrating changes (increase vs. decrease) in systolic and diastolic pressure within treatments on both an investigator and a composite basis. Data were also analyzed for the magnitude of pressor and depressor effects between treatments on both an investigator and a composite basis. The between treatment comparison was made on patients completing both cycles. The data were categorized as to whether the nabilone decrease was greater than the placebo decrease, the magnitude of the decrease was equal, or the placebo decrease was greater than the nabilone decrease. A Chi-Square analysis of the categorical data was then performed.

Protocol #28

Investigator 001

Twenty-four (24) patients, 8 male and 16 females were enrolled in the study. The frequency of the cancer types and therapies is given in Table 34.

Table 34: Frequency of Cancer Types in the 001 Population

<u>Type</u> <u>Evaluable</u>	<u>Number</u>	<u>(%)</u>
Lymphoma 4	8	(33)
Ovarian 1	4	(17)
Breast 2	4	(17)
Other 4	8	(33)

The most common chemotherapy regimen was Adriamycin, Cytosan and vincristine, the usual therapy for lymphoma. The evaluability of patients by chemotherapy and sequence (cycle) is given in Table 35.

Table 35: Chemotherapy by Evaluability & Sequence Group
(Table 1, Sponsor's Analysis, Vol 1.11, Pg 339)

<u>Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>
Cisplatin & other combinations	2	1	3	3	0	3
Other combinations without cisplatin	<u>4</u>	<u>4</u>	<u>8</u>	<u>3</u>	<u>7</u>	<u>10</u>
Total	6	5	11	6	7	13

Eleven patients were terminated early. The reasons for early termination are listed in Table 36.

Table 36: Reasons for Early Termination
(Table 8, Sponsor's Analysis, Vol. 1.11, pg 349)

<u>Reason</u>	<u># of Patients</u>	<u>Patient #s</u>
Adverse experience (nabilone)	4	104, 109, 118, 126
Adverse experience (placebo)	2	113, 115
Lack of efficacy (placebo)	2	116, 121
Lack of efficacy (nabilone)	1	120
Chemotherapy changed	1	106
Adverse experience (unknown relationship to nabilone)	<u>1</u>	105
Total	11	

There were two other patients considered inevaluable due to protocol violations. Both patients skipped a dose of nabilone due to side effect severity. According to the study criteria, missed doses constituted a protocol violation. I am in agreement that these two patients should be considered inevaluable.

Sixteen (16) patients (67%) were receiving one or more concomitant medications. Four "completers" received prednisone during both courses of chemotherapy.

The sequence groups were comparable with respect to previous chemotherapy, sex, and age. However, a significant sequence by chemotherapy interaction was detected, the result of an imbalance of cisplatin chemotherapies in group 1 versus group 2.

The means of the efficacy variables are listed in Table 37. Nabilone appeared to reduce nausea and vomiting although there was overlap between the treatment groups when the standard deviation was taken into account. The investigator's global impression of efficacy favored nabilone. The relative and absolute differences in side effect ratings by investigators suggest that nabilone treatment was differentiable from placebo and produced a moderate level of interference with patient's functioning. The former point strongly infers that the double-blind nature of this study may have been compromised. Consequently, I would place greater weight on the most objective criterion; i.e., vomiting frequency. The investigator's impressions may have been biased by the recognition of the treatment being administered.

Table 37:
Descriptive Statistics of
Daily Averages and Investigator's Global Impressions
(Table 2, Sponsor's Analysis Vol 1.11, Appendix E, pg 449)

		Daily Averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	7.17	2.20	0.67	2.83	1.33
	S.D.	4.92	0.69	0.82	1.72	1.21
n=6						
Placebo	Mean	12.00	2.80	0.40	4.20	0.00
	S.D.	3.67	0.45	0.55	0.84	0.00
n=5						
Cycle 2						
Nabilone	Mean	10.20	2.40	0.40	3.00	2.00
	S.D.	8.38	0.89	0.55	2.00	0.71
n=5						
Placebo	Mean	15.17	2.97	0.37	3.83	0.33
	S.D.	10.21	0.08	0.57	1.47	0.82
n=6						
Both Cycles						
Nabilone	Mean	8.55	2.29	0.55	2.91	1.64
	S.D.	6.53	0.76	0.69	1.76	1.03
n=11						
Placebo	Mean	13.73	2.89	0.38	4.00	0.18
	S.D.	7.76	0.30	0.53	1.18	0.60
n=11						

The analysis of variance on the ranked data is shown in Table 38. There were no residual effects. There is a trend towards a period (cycle) effect on the vomiting frequency data. The results show that a significant effect on vomiting, favoring nabilone occurred ($p = .028$, one tailed). Even if a two-tailed test were used, the p value would be 0.056. This shows a striking difference when one considers that the data analysis utilized 11 patients who completed the study with no protocol violations. A similar effect is seen for severity of nausea, again favoring nabilone ($p = .034$, one-tailed or .066, two-tailed).

Table 38:
Non-Parametric Crossover Analysis on Ranks
(Table 4, Sponsor's Analysis, Vol 1.11, Appendix E, pg 173)

	Mean Ranks		Z-value	P-value+
	Seq. Gp. 1 (n=6)	Seq. Gp. 2 (n=5)		
Residual Effects				
Freq. of Vomits - Average	6.17	5.80	-0.09	.500
- Day 1	6.17	5.80	-0.09	.500
Sev. of Nausea - Average	5.83	6.20	0.27	.500
- Day 1	5.92	6.10	0.18	.500
Food Intake - Average	6.33	5.60	-0.27	.500
- Day 1	6.33	5.60	-0.27	.500
Efficacy	5.58	6.50	0.55	.500
Adverse Effects	5.58	6.50	-0.55	.500
Treatment Effect				
Freq. of Vomits - Average	4.33	8.00	1.92	.028
- Day 1	4.33	8.00	1.92	.028
Sev. of Nausea - Average	4.42	7.90	1.83	.034
- Day 1	4.42	7.90	1.83	.034
Food Intake - Average	6.83	5.00	-0.82	.206
- Day 1	6.83	5.00	-0.82	.206
Efficacy	4.83	7.40	1.37	.085
Adverse Effects	8.08	3.50	-2.19	.014
Cycle Effect				
Freq. of Vomits - Average	4.75	7.50	-1.46	.144
- Day 1	4.75	7.50	-1.46	.144
Sev. of Nausea - Average	5.42	6.70	-0.73	.465
- Day 1	5.33	6.80	-0.82	.411
Food Intake - Average	6.83	5.00	-0.82	.411
- Day 1	6.83	5.00	-0.82	.411
Efficacy	5.83	6.20	-0.27	.500
Adverse Effects	5.17	7.00	1.00	.315

+Residual and Period Effects are two-tailed.
Treatment Effects are one-tailed.

Although the sponsor did not explain why a one-tailed analysis was chosen to examine treatment effects, I believe that since treatment superiority must be shown over placebo, the null hypothesis could be that a significant treatment effect exists favoring nabilone. Previous experience with nabilone in the "active control" studies would justify a one-tailed analysis.

The crossover frequency analysis of the categorical data (nabilone better, same, placebo better) failed to differentiate nabilone from placebo. The treatment effect for vomiting was $p = .262$. This is a likely result of the "collapsing" of the data down to 11 choices. The cycle 1 analysis of all patients also failed to differentiate treatment (efficacy) effects between nabilone and placebo. There was a significant increase in adverse effects in the nabilone group ($p = .009$, one-tailed). The failure to demonstrate treatment effects may be a result of the small numbers in the study groups. The nabilone vomiting frequency mean was less than half the placebo mean. The failure to demonstrate a treatment effect in cycle 1 patients may also be due to low vomiting frequency of three inevaluable (#104, 106 and 108) placebo patients. Had these three patients completed the crossover, the significant result attributed to nabilone may have been significantly diminished.

Investigator 002

At the time of NDA submission, this study had not been completed. Forty-two (42) patients had enrolled in the study at that time. There were 23 male and 19 females, in- and outpatients, between the ages of 17 and 63. The cancer types are listed in Table 39.

Table 39: Frequency of Cancer Types in the Study Population

<u>Type</u>	<u>Frequency</u>	<u>(%)</u>	<u>Evaluable</u>
Testicular	19	(45)	15
Breast	14	(33)	12
Other	9	(22)	6

The most common chemotherapy regimen was cisplatin in combination with Adriamycin, vinblastine and bleomycin, the usual treatment for testicular cancer. The next most frequent treatment was a one-day administration of Adriamycin, 5-fluorouracil and cyclophosphamide, the usual treatment for patients with breast cancer.

The cancer chemotherapy by evaluability and sequence group is presented in Table 40 (Table 1, Sponsor's Analysis, Vol. 1.12, pg 16).

Table 40: Cancer Chemotherapy by Evaluability & Sequence Group

<u>Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Gp. 1</u>	<u>Gp. 2</u>	<u>Total</u>	<u>Gp. 1</u>	<u>Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	7	11	18	2	1	3
Other combinations without cisplatin	<u>7</u>	<u>8</u>	<u>15</u>	<u>5</u>	<u>1</u>	<u>6</u>
Total	14	19	33	7	2	9

Thirty-three patients, 18 males and 15 females, were considered evaluable. Fourteen (42%) were in group 1 (nabilone on cycle 1) and 19 (58%) were in group 2 (placebo on cycle 1). Five patients (#220, 226, 234, and 240 - placebo cycle 2 and 237 - nabilone cycle 2) terminated "early" but were considered evaluable. The reasons for early study termination are listed in Table 41 (Table 8, Sponsor's Analysis, Vol. 1.12, pg 26).

Table 41: Reasons for Early Terminations

<u>Reason</u>	<u># Patients</u>	<u>Patient Numbers</u>
Drug-related (nabilone)	4	204, 205, 224, 237
Lack of efficacy (placebo)	4	220, 226, 234, 240
Lost to follow-up	1	211
Chemotherapy changed	1	243
Death due to cancer	<u>2</u>	213, 214
Total	12	

In addition to the early terminators, there were two patients (#222, 241) who completed the study but were ruled unevaluable due to differences in chemotherapy between the first and second cycles. I am in agreement that these two patients should have been excluded from the efficacy analysis. Further, I have evaluated the five early terminators that the sponsor deemed evaluable. I am in agreement that no protocol violations occurred and sufficient administration of both treatments was administered. Thus, I agree that 33/42 patients were evaluable.

One patient (#231) received prednisone on both chemotherapy cycles. I do not believe this could invalidate the study results.

There was a sequence group by evaluability interaction in the study; i.e., more patients were unevaluable in sequence group 1 than in sequence

group 2. The groups were comparable with respect to chemotherapy, previous chemotherapy, sex and age.

The results of the efficacy analysis are shown in Table 42. There is an apparent difference in the vomiting frequency and nausea severity scores across cycles for the placebo treatment. It is also interesting to note that the investigator rated nabilone more effective with a moderate effect on overall patient functioning.

Table 42:
Descriptive Statistics
Daily Averages and Investigator's Global Impressions
(Table 2, Sponsor's Analysis, Vol 1.12, Appendix E, pg 200)

		Daily averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	5.83	1.66	0.89	1.86	1.64
	S.D. n=14	5.77	0.98	0.73	0.95	0.50
Placebo	Mean	8.05	1.85	0.80	3.32	0.11
	S.D. n=19	9.17	0.91	0.57	1.34	0.32
Cycle 2						
Nabilone	Mean	2.93	0.85	0.81	1.74	1.63
	S.D. n=19	4.25	0.57	0.56	0.87	0.68
Placebo	Mean	19.83	2.38	0.41	4.21	0.00
	S.D. n=14	12.33	0.72	0.46	0.58	0.00
Both Cycles						
Nabilone	Mean	4.16	1.19	0.84	1.79	1.64
	S.D.	5.08	0.86	0.63	0.89	0.60
Placebo	Mean	13.05	2.08	0.63	3.70	0.06
	S.D. n=33	12.00	0.87	0.56	1.16	0.24

The analysis of variance data are presented in Table 43. Significant residual effects were observed for day 1 and average vomiting frequency, day 1 and average nausea severity, and investigator rated efficacy. There was a treatment-related effect of nabilone to increase food intake. Investigator-rated adverse effects were significantly greater ($p < .001$) for nabilone.

Table 43:
 Non-Parametric Crossover Analysis
 on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.12, Appendix E, pg 202)

		Mean Ranks		Z-value	P-value+
		Seq. Gp. 1 (n=14)	Seq. Gp. 2 (n=19)		
Residual Effects					
Freq. of Vomits	- Average	22.89	12.66	3.02	.003
	- Day 1	23.00	12.58	3.08	.002
Sev. of Nausea	- Average	22.25	13.13	2.70	.007
	- Day 1	21.68	13.55	2.40	.016
Food Intake	- Average	15.32	18.24	-0.84	.402
	- Day 1	14.93	18.53	-1.04	.299
Efficacy		20.43	14.47	1.77	.077
Adverse Effects		16.32	17.50	-0.33	.500
Treatment Effect					
Freq. of Vomits	- Average	8.64	23.16		
	- Day 1	8.86	23.00		
Sev. of Nausea	- Average	10.14	22.05		
	- Day 1	9.86	22.26		
Food Intake	- Average	20.96	14.08	2.04	.021
	- Day 1	19.57	15.11	1.33	.092
Efficacy		7.96	23.66		
Adverse Effects		26.50	10.00	4.86	< .001
Cycle Effect					
Freq. of Vomits	- Average	12.39	20.39		
	- Day 1	12.14	20.58		
Sev. of Nausea	- Average	19.11	15.45		
	- Day 1	19.64	15.05		
Food Intake	Average	20.18	14.66	1.64	.101
	- Day 1	20.04	14.76	1.57	.117
Efficacy		14.25	19.03		
Adverse Effects		17.96	16.29	0.51	.500

+Residual and Period Effects are two-tailed.
 Treatment Effects are one-tailed.

Results of the categorical analysis are shown in Table 44. Highly significant results favoring nabilone were demonstrated on the following parameters: day 1 ($p < .001$) and average vomiting frequency ($p < .001$), severity of nausea, day 1 ($p < .001$) and average ($p < .005$), investigator-rated efficacy ($p < .001$) and patient preference ($p < .001$). I asked Dr. Nevius for a consultation on this aspect of the Einhorn study. He agreed that the sponsor had followed the appropriate statistical dictum of not calculating treatment effects when a residual effect had been demonstrated. He recalculated the data, ignoring the residual effect. Highly significant results favoring nabilone were obtained. Thus, "ignoring the residual", one would obtain close agreement between the analysis of variance and the categorical analysis.

(Table 44
Crossover Frequency Analysis
(Tables 6A & 6B) Sponsor's Analysis, Vol 1.12, Appendix E, pg 205)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>	<u>Cycle</u> <u>Effect+</u>	<u>Treatment</u> <u>Effect++</u>
Freq. of vomits - Average					
Nabilone better	13	16	29	.5	<.001
Same	0	0	0		
Placebo better	1	3	4		
Freq. of vomits - Day 1					
Nabilone better	13	16	29	.5	<.001
Same	0	0	0		
Placebo better	1	3	4		
Severity of Nausea - Average					
Nabilone better	7	14	21	.5	<.005
Same	5	2	7		
Placebo better	2	3	5		
Severity of Nausea - Day 1					
Nabilone better	6	15	21	.5	<.001
Same	7	2	9		
Placebo better	1	2	3		
Food Intake - Average					
Nabilone better	7	6	13	.450	.057
Same	6	9	15		
Placebo better	1	4	5		
Food Intake - Day 1					
Nabilone Better	6	3	9	.265	.280
Same	7	12	19		
Placebo better	1	4	5		
Clinical Global Impressions					
Efficacy					
Nabilone better	13	14	27	.5	<.001
Same	1	4	5		
Placebo better	0	1	1		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	0	0	0	.5	<.001
Same	0	1	1		
Placebo better	14	18	32		
Patient's preference					
Nabilone better	14	16	30	.5	<.001
Same	0	2	2		
Placebo better	0	1	1		

+Two-Tailed, ++One-Tailed

The sponsor also performed a cycle 1 all-patients analysis (Table 45). Although there were no patient-rated variables which attained statistical significance, the investigator rated nabilone more efficacious ($p = .004$) and moderately affecting patient's ability to function.

Table 45 (Table 8, Sponsor's Analysis, Vol 1.12, Appendix E, pg 208)
Cycle 1 - All Patients

	<u>Freq. of Vomits</u>		<u>Severity of Nausea</u>		<u>Food Intake</u>		<u>Investigator's Global Impressions</u>	
	<u>Avg.</u>	<u>Day 1</u>	<u>Avg.</u>	<u>Day 1</u>	<u>Avg.</u>	<u>Day 1</u>	<u>Efficacy</u>	<u>Adv. Effects</u>
Nabilone								
(n=19) Mean	5.78	8.53	1.42	1.74	0.92	0.84	2.11	1.68
S.D.	5.98	7.86	0.86	1.10	0.70	0.76	1.05	0.48
Median	4.40	7.00	1.80	2.00	1.00	1.00	2.00	2.00
Placebo								
(n=19) Mean	8.02	9.68	1.83	2.21	0.79	0.79	3.32	0.11
S.D.	9.19	8.79	0.92	0.85	0.58	0.63	1.34	0.32
Median	2.60	7.00	2.00	2.00	1.00	1.00	4.00	0.00

Non-Parametric Analysis

Mean Rank

Nabilone	18.89	18.95	17.37	17.21	20.66	19.74	14.71	28.68
Placebo	20.11	20.05	21.63	21.79	18.34	19.26	24.29	10.32

Z-value	0.35	0.32	1.20	1.28	-0.63	-0.12	2.67	-5.08
P-value	.363	.374	.116	.099	.265	.453	.004	.001

*One-tailed

Investigator 003 (Frank Greco)

Fourteen (14) patients, 4 males and 10 females, were enrolled in this study. Patients were between the ages of 37 and 67 years old. The major tumor types were ovarian cancer (4/14), breast cancer (4/14), lung cancer (2/14) and other cancers (4/14). The most frequent chemotherapy regimen consisted of a one-day treatment of Adriamycin, Cytosan, hexamethylmelamine and cisplatin, given to 4 patients with ovarian cancer.

Five (5) patients, 1 male and 4 females, were considered evaluable for efficacy. There were 5 early terminations, 1 protocol deviation and 3 patients whose chemotherapy was changed in cycle 2.

Eight (8) patients received one or more concomitant medications. None of the five evaluable patients received prednisone or dexamethasone.

The small sample size precluded a statistical analysis. Of the evaluable patients, nabilone produced less vomiting, less nausea, a better investigator efficacy rating and higher incidence of side effects. Four of the five patients preferred nabilone.

Investigator 004

Sixteen (16) patients, 7 male and 9 female were enrolled in this study. Patients were between the ages of 16 and 80. Five (5) patients (31%) had breast cancer, 4 (25%) had lung cancer and 2 (13%) had lymphoma. The remaining five patients each had a different type of cancer.

The usual chemotherapy regimen was a one-day multiple drug administration. The most frequent combinations were Cytosan, Adriamycin, and one other additional agent (vincristine, 5-fluorouracil, cisplatin, methotrexate, etc.).

Eight (8) patients 4 male and 4 female were considered evaluable for the efficacy analysis. Four patients (#405, 412, 415 and 416) dropped out before completing the crossover due to adverse effects associated with nabilone. One (#401) patient dropped out due to lack of placebo efficacy. Patient #406 was dropped due to progressive disease. Patient #414 had her chemotherapy changed, making her unevaluable. Patient #418 was terminated before completion due to a flare-up of chronic rheumatoid arthritis.

Patient #402 received prednisone on both cycles of chemotherapy. I do not believe this compromises the results obtained in this patient. There was no difference in efficacy between nabilone and placebo in this patient.

The results obtained with the eight patients were not subjected to statistical analysis. However, visual inspection of the data supports nabilone superiority with respect to all patient and investigator-related efficacy variables. The investigators also rated nabilone as producing more side effects than placebo, which produced none. In spite of the greater side effect severity, 6/8 patients preferred nabilone.

The results of investigators 003 and 004 are tabulated and analyzed in the composite analysis.

I have one further comment that reinforces a previous remark about the compromise of the double-blind. It appears in both studies 003 and 004 that the blinding of the study was compromised by the ease of differentiability of the treatments, based on the nature and frequency of the side effects.

Investigator 005

This study was still in progress at the time of the NDA submission. The sponsor reported data on 58 patients, 25 male and 33 female, who enrolled in the study. Patient ages ranged from 17 to 79. Thirty-six (36) patients, 12 males and 24 females, with an average age of 53.6 years were considered evaluable for the study. The frequency of cancer type is listed in Table 46.

Table 46: Frequency of Cancer Type & Evaluability in Patient Population

<u>Type</u>	<u>Frequency</u>	<u>(%)</u>	<u>Evaluable</u>
Lung	21	(36)	10
Ovarian	11	(19)	9
Breast	10	(17)	10
Other	16	(28)	7

Cancers in the "other" category occurred with a frequency of 3 or less.

The sequence groups were comparable with respect to chemotherapy. The most common treatment was a combination of Adriamycin, cyclophosphamide, VP-16, vincristine or cisplatin. The cancer chemotherapy regimen by evaluability tabulation is listed in Table 47. (Table 1, Sponsor's Analysis, Vol. 1.13, pg 16).

Table 47: Cancer Chemotherapy by Evaluability & Sequence Group

<u>Chemotherapy Regimen</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Group 1</u>	<u>Group 1</u>	<u>Total</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>
Cisplatin and other combinations	4	8	12	7	4	11
Other combinations without cisplatin	<u>11</u>	<u>13</u>	<u>24</u>	<u>6</u>	<u>5</u>	<u>11</u>
Totals	15	21	36	13	9	22

Twenty (20) patients terminated the study before completing the crossover. The reasons for termination are given in Table 48 (Table 8, Sponsor's Analysis, Vol. 1.13, pg 26).

Table 48: Reasons for Early Terminations

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse effect (nabilone)	5	504, 516, 517, 566, 578
Adverse effect - no drug relationship)	1	577
Lack of efficacy (placebo)	1	508
Lack of efficacy (nabilone)	1	563
Patient decision	2	570, 575
Complicating decisions	1	1
Lost to follow-up	4	526, 533, 568, 574
Chemotherapy changed	4	519, 521, 541, 567
Death due to cancer	2	512, 564

Patient #504 actually was evaluable for 1 day of the crossover. Additionally, three patients (#507, 532, 536) who completed the crossover were judged unevaluable. I am in agreement that these three patients each had a protocol violation. Further, I agree that 36 patients were evaluable.

In this study, only one day of cancer chemotherapy was given. Forty-two patients received 4 mg of nabilone while 5 patients received only a 2 mg dose on the day of chemotherapy. All nabilone patients also received 2 mg on the evening prior to chemotherapy.

Sixteen (16) patients received one or more concomitant medications. One patient (#540) received prednisone during both cycles of the crossover. This patient was receiving prednisone as an adjunct to her chemotherapy for breast cancer. Serum chemistry analyses were not available for this patient. At any rate, one of 36 patients receiving prednisone is unlikely to bias the study.

Analysis of sequence group comparability revealed that the groups were comparable with respect to chemotherapy, previous chemotherapy, sex, and age.

The patient and investigator-rated descriptive variables are tabulated in Table 49 (Table 1, Sponsor's Analysis, Vol. 1.13, Appendix E, pg 177). The data suggest a potent antiemetic effect of nabilone. The side effect difference in the last column also suggests that the study blind was compromised.

Table 49
Descriptive Statistics
Efficacy and Safety Parameters

		<u>Freq. of Vomits</u>	<u>Severity of Nausea</u>	<u>Food Intake</u>	<u>Investigator's Global Impressions</u>	
					<u>Efficacy</u>	<u>Adverse Effects</u>
Cycle 1						
Nabilone	Mean	1.71a	0.87	1.67	1.93	1.07
	S.D.	3.95	1.23	1.29	1.33	0.70
n=15						
Placebo	Mean	7.33b	2.19	0.62	3.81	0.00
	S.D.	6.42	0.68	0.97	1.08	0.00
n=21						
Cycle 2						
Nabilone	Mean	3.94a	1.14	1.00	2.33	1.52
	S.D.	5.62	1.11	1.18	1.43	0.60
n=21						
Placebo	Mean	7.64b	2.33	0.33	3.60	0.07
	S.D.	5.75	0.82	0.49	0.83	0.26
n=15						
Both Cycles						
Nabilone	Mean	2.97c	1.03	1.28	2.17	1.33
	S.D.	5.01	1.11	1.26	1.38	0.72
n=36						
Placebo	Mean	7.47c	2.25	0.50	3.72	0.03
	S.D.	6.04	0.73	0.81	0.97	0.17
n=36						

a n=14, b n=18, c n=32

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Table 50:
Non-Parametric Crossover Analysis on Ranks
(Table 3, Sponsor's Analysis, Vol 1.13, Appendix E, pg 179)

	Mean Ranks		Z-value	F-value+
	Seq. Gp. 1 (n=15)	Seq. Gp. 2 (n=21)		
Residual Effects				
Freq. of Vomits	17.97	18.88	-0.24	.500
Sev. of Nausea	17.93	18.90	-0.26	.500
Food Intake	20.10	17.36	0.79	.432
Efficacy	16.63	19.83	-0.88	.378
Adverse Effects	15.73	20.48	-1.52	.188
Treatment Effect				
Freq. of Vomits	9.20	25.14	-4.46	<.001
Sev. of Nausea	9.27	25.10	-4.43	<.001
Food Intake	24.67	14.10	2.90	<.001
Efficacy	9.37	25.02	-4.38	<.001
Adverse Effects	28.63	11.26	4.89	<.001
Period Effect				
Freq. of Vomits	17.50	19.21	-0.47	.500
Sev. of Nausea	16.43	19.98	-0.98	.328
Food Intake	21.97	10.02	1.68	.092
Efficacy	17.37	19.31	-0.53	.500
Adverse Effects	15.37	20.74	-1.49	.136

+Residual and Period Effects are two-tailed.
Treatment Effects are one-tailed.

The analysis of variance of the ranked data is presented in Table 50. There were no residual effects observed on any of the five parameters. There was also no difference noted with respect to period effects or the parameters. A large treatment effect favoring nabilone occurred on every patient and investigator-rated efficacy variable ($p = .001$ or less). However, a significant difference in adverse effects was noted between nabilone and placebo ($p < .001$).

The results of the categorical analysis are listed in Table 51. Nabilone was rated superior to placebo on patient and investigator-rated efficacy variables. Further analysis showed nabilone to be equieffective against cisplatin versus non-cisplatin regimens (data not shown). Moreover, patients preferred nabilone to placebo ($p < .001$). This is of importance as nabilone was associated with a greater incidence and severity of side effects.

Table 51
Crossover Frequency Analysis

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>	<u>Cycle Effect+</u>	<u>Treatment Effect++</u>
Freq. of vomits					
Nabilone better	13	16	29	.5	.001
Same	0	3	3		
Placebo better	2	2	4		
Severity of Nausea					
Nabilone better	11	15	26	.5	.001
Same	4	4	8		
Placebo better	0	2	2		
Food Intake					
Nabilone better	10	9	19	.430	.004
Same	4	8	12		
Placebo better	1	4	5		
Clinical Global Impressions					
Efficacy					
Nabilone better	11	17	28	.5	.001
Same	3	2	5		
Placebo better	1	2	3		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	1	0	1	.5	.001
Same	3	0	3		
Placebo better	11	21	32		
Patient's preference					
Nabilone better	12	16	28	.5	.001
Same	2	3	5		
Placebo better	1	2	3		

+Two-Tailed, ++One-Tailed

The "all patients" cycle 1 analysis is presented in Table 52. Statistically significant results ($p = .01$ or less) favoring nabilone were observed for the patient-rated variables. Investigator-rated efficacy was also statistically significant, favoring nabilone ($p .001$). Adverse effects were rated as higher for nabilone ($p .001$) by the investigator. The adverse effect data were actually lower than comparable data in evaluable patients. (See Table 49)

Table 52:
 Descriptive Statistics and Test Results
 Cycle 1 - All Patients
 (Table 7, Sponsor's Analysis, Vol 1.13, Appendix E, pg 185)

		Freq. of Vomits	Severity of Nausea	Food Intake	Investigator's Global Impressions	
					Efficacy	Adverse Effects
Nabilone	Mean	3.74	0.83	1.30	2.05a	1.14a
	S.D.	7.54	1.07	1.18	1.36	0.89
	Median	1.00	0.00	1.00	1.00a	1.00a
Placebo	Mean	7.65b	2.26	0.56	3.93	0.04
	S.D.	6.03	0.71	0.89	1.07	0.19
	Median	7.00	2.00	0.00	4.00	0.00
Non-Parametric Analysis						
Mean Rank	Nabilone	17.61*	16.20	30.63	15.70	34.50
	Placebo	32.22*	33.43	21.13	32.57	17.26
Z-value		-3.52	-4.16	2.31	-4.10	4.21
P-value		.001	.001	.011	.001	.001

+One-tailed

^an=22, ^bn=23

Comments:

This study demonstrates a superior antiemetic effect of nabilone over placebo. Arguments regarding possible bias introduction due to dropouts are weakened by the highly significant effects favoring nabilone in the "all patients" cycle 1 analysis. Thus, this study provides persuasive evidence of an antiemetic effect without the possible bias incurred by dropping out "unevaluable" patients.

The patient population in this study was heterogeneous from a diagnostic standpoint. Consequently, no cancer type or chemotherapy regimen can be singled out as being highly susceptible to nabilone treatment. Further, I would doubt that an agency-conducted post-hoc analysis could determine a significant antiemetic effect in any of the cancer subgroups. This is, in part, due to the low numbers of patients in the subgroups (7 to 12). Thus, I would not recommend highlighting nabilone efficacy against, for example, cancer chemotherapy regimens for breast cancer.

The side effect profile of nabilone probably unmasked the double-blind in this study. Although this could lead to expectation effects, vomiting frequency is, for the most part, an objective parameter not without some psychological component. However, I believe the drug effect overshadows any benefit gained from an expectation of efficacy. Nausea and food intake ratings are more subjective, and would be more subject to bias. However, the potency of the effect argues that a drug component far overshadows any psychological component.

Investigator 006

This study was still in progress at the time of the NDA submission. Forty-five (45) patients, 20 males and 25 females, were enrolled in the study. Thirty-six patients, 16 males and 20 females with an average age of 56.2 years, were considered evaluable for efficacy. The frequency of cancer types is listed in Table 53.

Table 53: Frequency of Cancer Type & Evaluability in Patient Population

<u>Type</u>	<u>Frequency</u>	<u>(%)</u>	<u>Evaluable</u>
Breast	14	(31)	11
Lung	10	(22)	8
Ovarian	4	(9)	3
Other	17	(38)	14

Cancers in the "other" category occurred with a frequency of 3 or less.

The sequence groups were comparable with respect to chemotherapy. The most common treatments administered were Adriamycin, 5-Fluorouracil, cyclophosphamide, and methotrexate. These agents were used in various combinations to treat lung and breast cancer. The cancer chemotherapy by evaluability is listed in Table 54 (Table 1, Sponsor's Analysis, Vol. 1.13, pg 214).

Table 54: Cancer Chemotherapy by Evaluability & Sequence Group

<u>Chemotherapy Regimen</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>
Cisplatin and other combinations	6	2	8	0	2	2
Combinations without cisplatin	<u>13</u>	<u>15</u>	<u>28</u>	<u>4</u>	<u>3</u>	<u>7</u>
Totals	19	17	36	4	5	9

Ten (10) patients were terminated early. The reasons for early termination are given in Table 55 (Table 7), Sponsor's Analysis, Vol. 1.13, pg 223).

Table 55: Reasons for Early Terminations

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse effect (nabilone)	4	609, 625, 639, 704
Lack of efficacy (placebo)	3	603, 647, 649
Patient decision	2	619, 713
Death due to cancer	<u>1</u>	621
Total	10	

Patient #603 discontinued after his third placebo dose during the second cycle. Patient #625 was considered unevaluable due to a protocol violation. Thus, 36 patients were considered evaluable.

Chemotherapy regimens usually lasted only 1 day. Only 2 evaluable patients received more than 1 day of chemotherapy. However, data are displayed as both day 1 and "average" effects. All nabilone patients received a 2 mg dose on the evening preceding chemotherapy initiation and 40/41 received 4 mg of nabilone on day 1 of chemotherapy.

Thirty-nine (39) patients were receiving concomitant medications. Analgesics were the most common study drug administered. Two patients receive prednisone during both chemotherapy cycles. I do not believe these 2 patients could bias the results (in case there is an antiemetic effect of prednisone).

The sequence group comparisons noted that the groups were comparable with respect to chemotherapy, prior chemotherapy, sex and age.

The patient and investigator-rated variables are tabulated in Table 56 (Table 2, Sponsor's Analysis, Vol. 1.13, pg 364). Nabilone appears to exert a moderate antiemetic effect. The antinauseant effect of nabilone appears more potent, relative to the antiemetic effect. The investigator's impression of efficacy suggest nabilone is more efficacious; the average nabilone response equaled a good rating.

Table 56:
Descriptive Statistics
Daily Averages and Investigator's Global Impressions

		Daily averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	5.53	1.21	1.37	2.26	0.89
	S.D. n=19	7.97	1.13	0.83	1.15	0.57
Placebo	Mean	6.59	2.00	0.88	3.47	0.06
	S.D. n=17	10.39	1.06	0.78	1.18	0.24
Cycle 2						
Nabilone	Mean	3.41	1.29	1.29	2.00	1.12
	S.D. n=17	5.80	1.10	0.92	0.87	0.70
Placebo	Mean	7.12	2.11	0.95	3.58	0.05
	S.D. n=19	8.15	0.81	0.71	1.35	0.23
Both Cycles						
Nabilone	Mean	4.53	1.25	1.33	2.14	1.00
	S.D.	7.02	1.11	0.86	1.02	0.63
Placebo	Mean	6.87	2.06	0.92	3.53	0.06
	S.D. n=36	9.14	0.92	0.73	1.25	0.23

The analysis of variance data are presented in Table 57. There were no residual or period effects which reached statistical significance. There were patient-rated and investigator-rated efficacy variables which attained statistical significance, favoring nabilone. The following effects favored nabilone: day 1 ($p = .009$) and average vomiting frequency ($p = .008$), day 1 nausea severity ($p < .001$) and average severity of nausea ($p < .001$), day 1 food intake ($p = .016$) and average daily food intake ($p = .016$), and investigator-rated global efficacy ($p < .001$). Adverse effect incidence was more severe in the nabilone group ($p < .001$).

When the effects of nabilone on nausea and vomiting are compared, nabilone appears to exert a greater antinauseant effect relative to the antiemetic effect.

Table 57:
Non-Parametric Crossover Analysis on Ranks
(Table 4, Sponsor's Analysis, Vol 1.13, Appendix E, pg 366)

		Mean Ranks		Z-value	P-value+
		Seq. Gp. 1 (n=19)	Seq. Gp. 2 (n=17)		
Residual Effects					
Freq. of Vomits	- Average	19.21	17.71	-0.41	.500
	- Day 1	19.08	17.85	-0.33	.500
Sev. of Nausea	- Average	18.68	18.29	-0.10	.500
	- Day 1	18.68	18.29	-0.10	.500
Food Intake	- Average	18.66	18.32	-0.08	.500
	- Day 1	18.66	18.32	-0.08	.500
Efficacy		19.61	17.26	-0.65	.500
Adverse Effects		16.84	20.35	1.01	.311
Treatment Effect					
Freq. of Vomits	- Average	14.53	22.94	2.41	.008
	- Day 1	14.61	22.85	2.36	.009
Sev. of Nausea	- Average	13.16	24.47	3.23	<.001
	- Day 1	13.16	24.47	3.23	<.001
Food Intake	- Average	22.08	14.50	-2.14	.016
	- Day 1	22.08	14.50	-2.14	.016
Efficacy		12.29	25.44	3.76	<.001
Adverse Effects		25.95	10.18	-4.47	<.001
Period Effect					
Freq. of Vomits	- Average	19.34	17.56	-0.49	.500
	- Day 1	19.39	17.50	-0.52	.500
Sev. of Nausea	- Average	18.00	19.06	0.32	.500
	- Day 1	18.00	19.06	0.32	.500
Food Intake	Average	18.58	18.41	-0.03	.500
	- Day 1	18.58	18.41	-0.03	.500
Efficacy		18.76	18.21	-0.14	.500
Adverse Effects		17.00	20.18	0.92	.358

+Residual and Period Effects are two-tailed.
Treatment Effects are one-tailed.

The results of the categorical analysis are presented in Table 58 (Tables 6A&B, Sponsor's Analysis, Vol. 1.13, Appendix E, Pg 368-9). There was a trend ($p = .103$) favoring nabilone on the vomiting data. Highly significant effects favoring nabilone were noted for day 1 ($p < .001$) and average nausea severity ($p < .001$). Food intake also showed statistically significant effects, favoring nabilone ($p = .032$ for day 1 and average daily intake). Patients also preferred nabilone 25 to 9 ($p = .007$); a higher incidence of adverse events was recorded in the nabilone group.

Table 58
Crossover Frequency Analysis

	<u>Frequency of Patients</u>			<u>F-Value</u>	
	<u>Seq.</u>	<u>Seq.</u>	<u>Total</u>	<u>Cycle</u>	<u>Treatment</u>
	<u>Gp. 1</u>	<u>Gp. 2</u>		<u>Effect+</u>	<u>Effect++</u>
Freq. of vomits - Average					
Nabilone better	10	10	20	.500	.103
Same	3	2	5		
Placebo better	6	5	11		
Freq. of vomits - Day 1					
Nabilone better	10	10	20	.500	.103
Same	3	2	5		
Placebo better	6	5	11		
Severity of Nausea - Average					
Nabilone better	12	11	23	.500	<.001
Same	5	4	9		
Placebo better	2	2	4		
Severity of Nausea - Day 1					
Nabilone better	12	11	23	.500	<.001
Same	5	4	9		
Placebo better	2	2	4		
Food Intake - Average					
Nabilone better	6	6	12	.500	.032
Same	12	9	21		
Placebo better	1	2	3		
Food Intake - Day 1					
Nabilone Better	6	6	12	.500	.032
Same	12	9	21		
Placebo better	1	2	3		
Clinical Global Impressions					
Efficacy					
Nabilone better	13	12	25	.500	<.001
Same	3	2	5		
Placebo better	3	3	6		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	1	1	2	.500	<.001
Same	3	2	5		
Placebo better	15	14	29		
Patient's preference					
Nabilone better	15	12	25	.500	.007
Same	2	0	2		
Placebo better	4	5	9		

+Two-Tailed, ++One-Tailed

The results of the "all patients" cycle 1 analysis are shown in Table 59 (Table 8, Sponsor's Analysis, Vol. 1.13, Appendix E, pg 372). A trend favoring nabilone on day 1 vomiting frequency is evident (p = .083). In fact, the same data with 3 or 4 more patients/group would attain significance at the p = .05 level. As this study was in progress at the time of the NDA submission, the results of the first period may attain significance when an update of the completed study is submitted.

Nabilone's effect attained statistical significance on day 1 (p = .006) and average nausea severity (p = .017), day 1 food intake (p = .024) and average food intake (p = .047) and investigator-rated global efficacy (p = .005). The results suggest that the investigator may have keyed on nausea and food intake rather than vomiting frequency in assessing efficacy.

Table 59:
Cycle 1 - All Patients Analysis
(Table 8, Sponsor's Analysis, Vol 1.12, Appendix E, pg 208)

	<u>Freq. of Vomits</u>		<u>Severity of Nausea</u>		<u>Food Intake</u>		<u>Investigator's Global Impressions</u>	
	<u>Avg.</u>	<u>Day 1</u>	<u>Avg.</u>	<u>Day 1</u>	<u>Avg.</u>	<u>Day 1</u>	<u>Efficacy</u>	<u>Adv. Effects</u>
Nabilone								
(n=21) Mean	5.48	5.48	1.26	1.26	1.35	1.35	2.48	1.13
S.D.	7.64	7.64	1.10	1.10	0.78	0.78	1.16	0.81
Median	1.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00
Placebo								
(n=21) Mean	9.13*	10.85*	2.00	2.19	0.89	0.81	3.52	0.05
S.D.	15.70	16.07	1.06	1.03	0.81	0.75	1.29	0.22
Median	4.00	4.00	2.00	3.00	1.00	1.00	4.00	0.00
Non-Parametric Analysis								
Mean Rank								
Nabilone	20.52	19.96	18.61	17.61	25.63	26.20	17.72	30.78
Placebo	24.67	25.29	26.76	27.86	19.07	18.45	27.74	13.43
Z-value	1.08	1.39	2.11	2.66	-1.68	-1.99	2.60	-4.46
P-value+	.140	.083	.017	.006	.047	.024	.005	<.001

+One-tailed
*n=20

Comments:

The results of this study demonstrate a salutary effect of nabilone over placebo on nausea and vomiting associated with cancer chemotherapy. The effect on nausea was more notable than the effect on vomiting. However, the analysis of variance of the ranked data found statistically significant effects favoring nabilone on the emesis variables.

As in the other studies reviewed, the side effect profile probably unmasked the study blind. Thus, more credence should be given to the vomiting frequency data and less to the patient-rated nausea variables. Consequently, the results of the study are somewhat diminished in importance as a greater anti-nauseant effect was observed. However, the analysis of variance demonstrated a significant ($p = .008$) effect of nabilone on vomiting frequency. In the cycle 1 all patients analysis, a nearly-significant ($p = .085$) result was obtained. The results of the study may be more positive for nabilone when all the data are submitted.

Composite analysis - Protocol 28

The sponsor analyzed the data from the six centers which comprised the study. Of the 199 patients that were entered, 129 patients were evaluable. A significant sequence group by evaluability effect occurred, i.e., more patients were unevaluable in sequence group 1 than in group 2.

Analysis of the groups with respect to treatment parameters and patient demographics revealed several statistically significant investigator interactions. A significant investigator by evaluability effect was noted ($p < .001$); the proportion of evaluable patients varied significantly across investigators. Investigator interactions were also noted for chemotherapy ($p = .036$), prior chemotherapy ($p = .012$), evaluability by prior chemotherapy ($p = .014$), and age ($p < .001$).

Comment:

In terms of clinical ramifications, this strongly suggests that only general conclusions could be made in the composite analysis. The treatment variables exhibit significant heterogeneity, making conclusions about treatment versus cancer type chemotherapy or treatment efficacy in the face of previous chemotherapy a hazardous undertaking. Consequently, the composite results can only be discussed in a general way; i.e., whether nabilone was superior to placebo treatment in the treatment of nausea and emesis associated with (a variety of) cancer chemotherapy regimens. Given the caveat that a composite analysis of this study could only be used to support a general labeling claim, I have no objections to the results being combined and analyzed.

The cancer type by evaluability is listed in Table 60 (Table 1, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 312). The rank order of evaluable cancer types was: breast > lung > testis > ovary > lymphoma > Hodgkins. All other evaluable cancers occurred with a frequency of 3 or less.

Comment:

The patient population differs from those in the two active control trials in which nabilone demonstrated efficacy. Patients with testicular cancer were the predominant patient group in those studies.

Table 60
Comparison of Sequence Groups and
Evaluability Groups for Type of Cancer

Chemotherapy Regimen	Evaluable			Unevaluable		
	Seq. Group 1	Seq. Group 2	Total	Seq. Group 1	Seq. Group 2	Total
Adenocarcinoma	1	0	1			
Bladder	0	2	2	0	1	2
Bone				2	0	2
Breast	17	20	37	9	6	15
Cervix				1	0	1
Colon	1	1	2	1	0	1
Connective Tissue	0	3	3			
Esophagus				1	0	1
Fallopian Tube	0	1	1	1	0	1
Germinoma	0	1	1			
Hodgkin's	3	2	5	1	1	2
Kidney	0	1	1			
Larynx	1	0	1	1	1	2
Leukemia				1	0	1
Lung	8	15	23	8	7	15
Lymphoma	4	4	8	5	2	7
Lymphoma Non-Hodgkin's				0	1	1
Melanoma	1	1	2	0	2	2
Mesothelioma	0	1	1			
Ovary	7	8	15	5	3	8
Pancreas	1	0	1			
Parotoid Gland				0	1	1
Pharynx				1	0	1
Prostate	1	2	3			
Rectum	1	0	1			
Squamous Cell				0	1	1
Stomach	1	0	1			
Testis	8	10	18	4	1	5
Thyroid	1	0	1			
Uterus	1	0	1	0	1	1
Unknown				0	1	1
Total	57	72	129	41	29	70

Forty-five of the 129 evaluable patients received cisplatin-based regimens. However, investigator #002 had a residual effect for vomiting in his study which caused 18 cisplatin patients and 15 non-cisplatin (33 total) patients to be dropped from the analysis. Therefore, only 27 of 96 evaluable patients received cisplatin in the analysis of certain efficacy variables (vide infra). This explains why results will be expressed as both with an "n" of 129 and an "n" of 96. The chemotherapy distribution also suggests that nabilone would need to be effective in noncisplatin-based regimens. This takes on more importance than usual because nabilone has already proved efficacious against cisplatin in active controlled trials (vide supra).

The results of the patient and investigator-rated results are tabulated in Table 61 as a function of investigator. In each case, the nabilone treatment means favor a superior antiemetic and antinauseant effect of nabilone. The investigators all rated nabilone as being both efficacious and producing a higher incidence of adverse events.

Table 61:
Means

(Table 3C, Sponsor's Analysis, Vol 1.11, Appendix E, pg 319)

Drug	Investigator	n	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
			Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone	001	11	8.55	8.55	2.29	2.27	0.55	0.55	2.91	1.64
	002	33	4.16	5.58	1.19	1.45	0.84	0.75	1.79	1.64
	003	5	10.27	15.20	1.73	2.00	1.20	1.20	2.20	1.00
	004	8	2.33 ^a	2.33 ^a	1.75	1.75	1.00	1.00	1.63	1.38
	005	36	2.97 ^b	2.97 ^b	1.03	1.03	1.28	1.28	2.17	1.33
	006	36	4.53	4.53	1.25	1.25	1.33	1.33	2.14	1.00
Composite	129	451 ^c	4.51 ^c	5.09 ^c	1.31	1.39	1.10	1.09	2.09	1.33
	(96)	(4.91) ^d	(4.91) ^d							
Placebo	001	11	13.00	13.73	2.89	2.91	0.38	0.36	4.00	0.18
	002	33	13.05	15.03	2.08	2.39	0.63	0.61	3.70	0.06
	003	5	34.60	36.80	2.67	2.80	0.40	0.40	3.40	0.20
	004	8	14.83 ^a	14.83 ^a	2.75	2.75	0.63	0.63	4.38	0.00
	005	36	7.47 ^b	7.47 ^b	2.25	2.25	0.50	0.50	3.72	0.03
	006	36	6.87	6.86	2.06	2.06	0.92	0.92	3.53	0.06
Composite	129	1081 ^c	10.81 ^c	11.43 ^c	2.25	2.34	0.64	0.64	3.71	0.06
	(96)	(9.99) ^d	(9.99) ^d	(10.11) ^d						

^an=6, ^bn=32, ^cn=123, ^dn=90
() = without investigator 002

The composite analysis of variance is presented in Table 62 (Table 5, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 323). There is a significant investigator effect in the analysis of residuals for all patient-rated variables and an investigator by residual interaction for day 1 and average vomiting frequency. When the sponsor removed investigator #002 from the analysis, the interaction disappeared. Thus, the treatment effect for vomiting frequency was calculated after omitting the data from investigator #002. There was a significant investigator effect, suggesting a differential response on day 1 vomiting across investigators. There were investigator x treatment interactions for day 1 ($p = .019$) and average vomiting frequency ($p = .01$), and adverse effects ($p = .042$). The treatment effects were calculated by dividing the treatment SS by the investigator x treatment SS. Treatment effects favoring nabilone at the $p = .02$ level or less were noted on all patient- and investigator-rated efficacy variables. Nabilone also produced a greater incidence of adverse effects ($p < .001$).

Table 62
Crossover Analysis of Variance on Ranks

Residual Effect	Investigator		Residual		Inv. x Residual		Error	
	S.S.a	P	S.S.b	P	S.S.a	P	S.S.c	
Freq. of Vomits - Average	21997	.003	112	.500	13070	.054	136118	
- Day 1	30688	.001	2	.500	12929	.047	130455	
Sev. of Nausea - Average	22284	.003	404	.500	9229	.170	136717	
- Day 1	27244	.001	298	.500	9124	.168	134611	
Food Intake - Average	14935	.052	1181	.346	2532	.500	154316	
- Day 1	15944	.036	961	.390	3395	.500	151018	
Efficacy	5292	.500	1245	.336	9328	.228	155843	
Adverse Effects	21934	.001	216	.500	9445	.095	115173	
Removing INV = 002								
Freq. of Vomits - Average	10467 ^d	.006	563	.360	1781 ^d	.500	57256 ^e	
- Day 1	11608 ^d	.003	299	.500	1804 ^d	.500	56603 ^d	
Treatment Effect								
	<u>Investigator</u>		<u>Treatment</u>		<u>Inv. x Treatment</u>		<u>Error</u>	
	S.S.a	P	S.S.b	P	S.S.a	P	S.S.c	
Freq. of Vomits - Average	1384 ^d	.476	19969	.010*	5525 ^d	.010		
3355 ^e	5473 ^d	.011	10647	.021*	4880 ^b	.019	33729 ^e	
Sev. of Nausea - Average	1603	.500	29998	<.001	3036	.500	94793	
- Day 1	2812	.500	26593	<.001	3001	.500	91510	
Food Intake - Average	4350	.500	12463	<.001	3799	.500	118295	
- Day 1	4534	.478	11234	<.001	4716	.454	116427	
Efficacy	3484	.407	32274	<.001	4510	.258	79645	
Adverse Effects	2490	.290	46996	<.001*	4760	.042	46660	

a - d.f.=5, b - d.f.=1, c - d.f.=117, d - d.f.=4, e - d.f.=86
 *Tested against Inv x Treatment +Omitting Investigator 002
 All p-values are two-tailed except for the treatment effect which is one-tailed.

The results of the all patients cycle 1 means are shown in Table 63 (Table 7A, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 325). When compared to the evaluable patient's data shown in Table 61, no significant changes are apparent. Thus, one would predict that significant differences favoring nabilone would be found. This is indeed the case. Table 64 shows the results of the analysis of variance on the all patients cycle 1 data. Statistically significant differences favoring nabilone were observed on the following parameters: day 1 (p = .007) and average vomits (p = .006), day 1 (p < .001) and average nausea severity (p .001), and investigator-rated efficacy (p < .001). The investigators also assigned a higher side effect incidence to nabilone (p < .001).

Table 63
Cycle 1 - All Patients
Means

Drug	Investigator n	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions		
		Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects	
Nabilone	001	9	5.27	5.22	2.07	2.00	0.69	0.78	3.00	1.22
	002	19	5.78	8.53	1.42	1.74	0.92	0.84	2.11	1.68
	003	2	11.17	23.50	1.33	2.00	0.50	2.50	2.50	1.50
	004	5	10.40	10.40	1.80	1.80	0.80	0.80	2.60	1.20
	005	23	3.74	3.74	0.83	0.83	1.30	1.30	2.05 ^b	1.14 ^b
	006	23	5.48	5.48	1.26	1.26	1.35	1.35	2.48	1.13
Composite	81	5.48	6.42	1.30	1.38	1.11	1.10	2.34 ^e	1.29 ^e	
Compazine	001	11	11.80	12.73	2.20	2.27	0.98	0.91	3.64	0.09
	002	19	8.02	9.68	1.83	2.21	0.79	0.79	3.32	0.11
	003	7	23.86	23.86	2.29	2.29	0.57	0.57	3.71	0.14
	004	7	21.40 ^a	21.40 ^a	2.86	2.86	0.43	0.43	4.71	0.00
	005	27	7.65 ^c	7.65 ^c	2.26	2.26	0.56	0.56	3.93	0.04
	006	21	9.13	10.85 ^d	2.00	2.19	0.89	0.81	3.52	0.05
Composite	92	10.77 ^f	11.66 ^f	2.15	2.28	0.72	0.70	3.72	0.07	

a_n=5, b_n=22, c_n=23, d_n=20, e_n=80, f_n=85

Table 64:
 Cycle 1 - All Patients
 Analysis of Variance on The Ranks
 (Table 8, Sponsor's Analysis, Vol 1.11, Appendix E, pg 326)

	<u>Investigator</u>	<u>Treatment</u>	<u>Inv. x Treatment</u>	<u>Error</u>
	<u>S.S.a</u>	<u>S.S.b</u>	<u>S.S.a</u>	<u>S.S.c</u>
	<u>P</u>	<u>P</u>	<u>P</u>	
Freq. of Vomits - Average	22182	13873	18721	352217
- Day 1	27961	13133	18758	346184
Sev. of Nausea - Average	22292	33984	16220	307421
- Day 1	20275	25874	10435	302378
Food Intake - Average	14374	4446	11329	343227
- Day 1	11827	4757	11199	334242
Efficacy	12746	53736	10661	284928d
Adverse Effects	8293	114377	4468	125810d

ad.f.=5, bd.f.=1, Cd.f.=161, Qd.f.=160

All p-values are two-tailed except for the treatment effect which is one-tailed.

Further, the results of the all patients' cycle 1 analysis are in general agreement with the antinauseant and antiemetic effect of nabilone demonstrated in the analysis of the evaluable patients who completed both cycles of the crossover. This finding tends to negate any suspicion of unintentional or systematic bias that may have been introduced by evaluating only patients who completed the crossover.

The results of the patient preference questions are tabulated and analyzed in Table 65 (Table 9B, Sponsor's Analysis, Vol 1.11, Appendix C, pg 330). Nabilone was preferred by evaluable patients (p .001) and all (evaluable and unevaluable) patients (p .001).

Table 65
Analysis of Patient Preference Frequencies

Evaluable Patients

<u>Source of Variation</u>	<u>d.f.</u>	<u>x²</u>	<u>p</u>
Investigator x Cycle	5	2.63	.500
Treatment	1	28.13	.001
Inv. x Treatment	5	9.52	.090

Evaluable and Unevaluable Patients

<u>Source of Variation</u>	<u>d.f.</u>	<u>x²</u>	<u>p</u>
Evaluability x Seq. Gp. 1	1	0.29	.500
Treatment	1	149.98	.001

Comments:

The composite results of the multicentered study of both the evaluable group and the cycle 1 all patients analysis provide persuasive evidence of a highly significant antinauseant and antiemetic effect of nabilone. The effect of nabilone of food intake is less striking.

The study was also analyzed by each component (investigator). Only 4 of 6 studies were analyzed statistically (#001, 002, 005 and 006). Studies 002, 005, and 006 were still in progress at the time of the NDA submission. We will ask the sponsor for all data as part of the safety update. The results are so impressive that I do not believe that further documentation of efficacy is necessary. However, the sponsor should be asked to subdivide the non-cisplatin based chemotherapies into their

respective groups and perform a categorical analysis of patient perceptions (nabilone better, same, placebo better). This may provide a useful analysis to answer our consultant's (Dr. Johnson) suggestion that the drug demonstrate efficacy against a wide variety of chemotherapy regimens, viz, DTIC-based regimens, Adriamycin-based regimens, Cytosan-based regimens without Adriamycin, and any other regimen occurring with such frequency as to make evaluation meaningful.

Investigator #002) had a residual effect that invalidated the analysis of variance. However, the categorical analysis was performed in this study, highly significant results favoring nabilone were evident. If one accepts the categorical analysis in this study, then nabilone demonstrated efficacy in 4/4 analyzed centers. The results obtained in the other two centers were not analyzed due to the small numbers of evaluable patients. The data trends are in agreement with those of the 4 analyzed studies.

Again, as in all the studies reviewed, I have no doubt that the double-blind was not maintained due to the unmistakable psychotropic effects of nabilone. This does not, in my opinion, negate the study results.

Conclusion:

This adequate and well-controlled study demonstrates the efficacy of nabilone against the nausea and vomiting associated with cancer chemotherapy. Of equal importance, the studies involved a different patient population (see Table 58) than those who participated in the trials which utilized active controls (Protocols 9 and 20).

(Note: patients in Protocol 28 were not included in the vomiting frequency analysis. This removed 15 patients with testicular cancer, 12 patients with breast cancer, and 6 "other" patients from the analysis).

Overall conclusions:

The sponsor has demonstrated substantial evidence of the effectiveness of nabilone as an antiemetic adjunct in cancer chemotherapy regimen in both compazine- and placebo-controlled trials. The Einhorn studies in Protocols 9 and 20 demonstrate nabilone's effectiveness vis a vis compazine in these adequate and well controlled trials. The placebo controlled trial (28) had 3 of 4 centers demonstrating nabilone's superiority over placebo. The fourth of four placebo controlled trials demonstrated nabilone's superiority in the categorical data analysis.

Nabilone was fairly well tolerated by the study participants insofar as there was both numerical and statistical superiority favoring nabilone over compazine or placebo as the drug preferred by patients.

There is sufficient evidence to recommend that nabilone be considered an effective antiemetic agent. A favorable benefit/risk judgment will require a supervisory overview as the safety review was done by a second reviewer, Dr. Hanson.

Tolerance to the subjective CNS effects of CESAMET^(R) was noted in studies employing normal volunteers. A partial loss of tolerance occurred within one week after cessation of nabilone. I looked for signs of diminished drug effect in the clinical trials and didn't see any. It may not occur to any significant degree in the 1 to 4 mg/day dose range. Alternatively, tolerance may be offset by a decreasing emetic stimulus over a chemotherapy course. I also don't believe that tolerance will be a problem with repeat cycles of therapy as 3 to 6 week washout periods between cycles should restore full sensitivity, even if tolerance occurs within a chemotherapy cycle.

The abuse potential of nabilone has been evaluated in preclinical and clinical studies. My drug abuse evaluation of 11/23/82 reached several conclusions about nabilone: 1) it is pharmacologically similar to delta-9-tetrahydrocannabinol; 2) a substantial overlap exists between the antiemetic dose range and the dose range producing subjective effects; 3) it has a high potential for abuse; and 4) it should be controlled in the same schedule of the Controlled Substances Act as delta-9-tetrahydrocannabinol (Schedule II upon marketing approval). The Drug Abuse Advisory Committee recommended on April 28, 1983 that nabilone be scheduled in CSA Schedule III at the time of marketing approval. I am recommending that the Division reject the Committee's advice and propose nabilone for CSA II. Accordingly, I will draft the scheduling documents to propose a Schedule II classification of nabilone.

f. Labeling review:

The proposed labeling is, in many sections, unacceptable. I have specific recommendations for the labeling sections to be incorporated into the draft approvable letter (vide infra). These will be communicated to Drs. Tocus, Hanson, Katz and Leber in the formulation of the draft labeling.

g. Summary of recommendations:

(1) Scientific

- (a) Nabilone has demonstrated efficacy as an antiemetic against chemotherapy-induced nausea and vomiting. However, the unsubmitted data from the placebo-controlled study should be added to that previously submitted. A composite or individual (site) analysis of variance would be unnecessary

although of interest. A categorical analysis of noncisplatin-based chemotherapy regimens should be conducted (Adriamycin-based regimens, DTIC-based regimens, and any other regimens which have sufficient data to allow a meaningful analysis) in order to demonstrate a salutary effect of nabilone on several major chemotherapy regimens.

(b) Nabilone should be considered for CSA Schedule II as its abuse potential is equal to that of delta-9-THC.

(2) Administrative

(a) Draft labeling and drafting of the anticipated Summary Basis of Approval be undertaken rapidly if and when the supervisory review makes a finding of favorable risk/benefit is found.

Frank J. Vocci Jr.
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CC:
NDA Orig
HFN-120
HFN-120/FVocci/10/12;11/29;12/6/84
FT:dca/10/24;11/30;12/6;12/16/84
DOC #2138C

PHARM REVIEW

JAN 4 1983

Review and Evaluation of Pharmacology and Toxicology Data of
NDA 18-677
DAS Consult Review of the August 17, 1982 Submission

The sponsor is Lilly Research Laboratories, Indianapolis, Indiana 46285.

The sponsor has appended summaries of two studies:

1. Subjective and psychomotor effects and abuse liability of nabilone as compared to delta-9-tetrahydrocannabinol, M.D., Ph.D.; and
2. Comparative assessment of reinforcing properties of nabilone and marijuana.

Portions of protocol #31 (the _____ study) and protocol #33 (the _____ study) have been previously reviewed (see Voccl review of 10/26/82). With respect to the _____ study, the physiological and subjective effects data were reported and previously reviewed. At the time, however, the psychomotor effects data were incomplete and have now just been submitted. The following psychomotor tests were used in 6 subjects who received either oral or intravenous delta-9-THC or nabilone and placebo: wobble board testing, pursuit meter, delayed auditory feedback performance, and a mirror drawing test.

The wobble board test employs a sensing system capable of measuring angular displacement of a platform upon which a subject stands. Subjects' balance-seeking movements are detected by a linear variable differential transformer and quantitated by an electronic counter in arbitrary numerical units. Subjects were tested for standing steadiness for 5 consecutive periods of 10 seconds each for each of the following conditions: eyes open; eyes closed; eyes open, vibrator on; and eyes closed, vibrator on. Increasing score corresponded to decreasing standing steadiness.

The second test, the pursuit meter, was used to measure attentive motor performance and hand-eye coordination. This instrument consisted of a Hewlett-Packard dual beam oscilloscope and a steering wheel which the subject used to control one of the oscilloscope beams. The subject's task was to track the sine wave pattern displayed by the other beam. An error score was calculated between the instrumental problem and the motor response of the subject and was digitally displayed. Increasing score corresponded to decreasing ability to perform this task.

A delayed auditory feedback test was used as a measurement of mental performance. Subjects spoke into a microphone which was fed into a tape recorder; a playback head was mounted so that subjects received an audio feedback into their headphones at a 0.28 second delay. The intensity of sound was monitored to maintain it at a level slightly higher than a comfortable

listening level in order that the subject could not easily ignore it. Three different tests were used to measure the subject's performance. In the first task, the subject read a passage from "Aristotle's Selections" in reverse. Both total number of words read and number of errors were recorded. The subject also read aloud from a list of subtraction word problems and provided the final answer. Both the number of problems completed and accuracy were measured. For the Color Differentiation Test, subject was given a card which had color names printed on it in different colors on a black background. The color name was never the same as the color in which the word was printed. The subject was instructed to read the name of the first word but state the color in which the second word was printed as to continue in this alternate pattern. Both the number of color problems completed and accuracy were measured. There were seven variations for each of these three tests. In order to reduce familiarization with the testing material or problems, each variation was used no more than once during any experimental session, but the same variations were used in the same order at all experimental sessions of the study.

4. Antianxiety effects were evaluated using the mirror drawing test. A concentric double-star pattern was used for this test. The two stars outlined a narrow pathway which the subject was required to trace by means of its image as seen in a mirror. The figure itself and the hand and arm employed were concealed from direct view by means of a simple screen so that all visual guidance was obtained solely from the reflection in the mirror. Crossing or touching lines constituted an error. Both speed and accuracy were emphasized in instructions to subject; ~~but~~ the number of times a subject could trace the pattern in a two-minute period and the number of errors during that period were recorded.

The study design was of a double-blind, randomized type with a repeated measures-blocking over subjects. During a 3-week period, with treatments separated by at least 3 days, each subject received each of the 5 treatments including:

1. placebo only administered both orally and intravenously;
2. 2 mg nabilone p.o. and placebo i.v.;
3. 17.5 mgs THC p.o. and placebo i.v.;
4. placebo p.o. and 0.25 mgs nabilone i.v.; and
5. placebo p.o. and 2.7 mgs of THC i.v.

The greatest results observed in the wobble board test were seen with the i.v. THC. However, the results were not significantly different from oral THC or intravenous nabilone. Additionally, at the 1-hour time point, the effects of

oral nabilone were not significantly different from intravenous nabilone or placebo. At the 2-hour score point, none of the treatment differences were significantly different from one another. At the 4-hour time point, the nabilone oral had its greatest ~~magnitude~~ of effect, although none of the treatments were significantly different from one another. These results suggest a slight differentiation between the onset and duration of a "high" and the greatest effects on psychomotor performance. Had the results been carried further, that is at 5-8 hours, a greater effect on wobble board performance may have been observed.

In the pursuit meter test, the greatest impairment was observed at 1 hour following i.v. nabilone. The effect of the i.v. THC at 1 hour was similar although neither score was significantly different from placebo. The results were confounded somewhat by a learning factor which results in improved performance despite practice sessions. When subjects were asked whether the intravenous treatments would impair their driving performance, 5 of 6 who received i.v. THC and 4 of 6 who received i.v. nabilone responded affirmatively.

The greatest impairments following each of the oral treatments occurred at the 4-hour testing period, at which time the mean increase following both oral THC and oral nabilone were significantly different from the mean decrease in score following placebo. When subjects were asked if they felt their driving would be impaired, 4 of 6 who received oral THC and 2 of 6 who received oral nabilone responded affirmatively. No subject felt his driving would be impaired after receiving placebo.

In the delayed auditory feedback paradigm, the greatest mean decrease in the number of color differentiation problems completed was observed following i.v. nabilone, although the mean decrease was not statistically significantly different from the mean increases observed following placebo administration. Performance under i.v. THC administration did not differ significantly from the placebo performance. The 4% decrease in accuracy of color differentiation problems completed 2 hours following i.v. THC was significantly different from both the 1% increase in accuracy following i.v. nabilone and the absence of change from the baseline testing period following placebo. With respect to the oral drug administrations, performance following either THC or nabilone did not differ significantly from performance following placebo at any time period. At the 4-hour time point, the decrease in subtraction performance observed with oral nabilone was significantly different from the placebo and oral THC responses.

No other statistically significant changes across groups were observed in the other psychomotor tests.

The additional data supplied by Dr. _____ to Lilly consisted of the following information: _____ Medical Index Questionnaire, ADARC Background

Questionnaire, Rating Scales of "High", PCMS, questionnaires regarding whether the capsules or cigarettes were thought to be active drug or placebo, Mood Status Reports, results of drug abuse screens, and serum prolactin concentrations before and after placebo and active drugs. The results are consistent with the previous stated conclusions of the investigator.

Evaluation:

As stated previously in the Vocci review of 10/26/82, both these studies have a common flaw; that is, conclusions are being drawn across drugs using single point assay determinations. The problem with this approach is that equipotent doses must be used in order to ascertain changes in intrinsic activity. Thus, changes in one test versus another may be qualitatively examined but quantitative comparisons can not be made. Seen in this light, it is obvious that both oral and i.v. nabilone and oral and i.v. delta-9-THC cause impairments in psychomotor performance. With the i.v. dosage forms, the largest magnitude of effect is generally observed at the early time points, i.e., 1 to 2 hours, whereas with the oral dosage forms, particularly in nabilone, the greatest effect was often observed at the 4-hour time point. These results suggest that there may be a slight time differentiation between the peak "high" effect of oral nabilone or oral THC, and the greatest effect on psychomotor performance.

The study states that the conclusions are essentially the same as those which were previously reported. The sponsors' most significant finding was that marijuana was preferred over THC and nabilone. No subject picked nabilone as a preferred drug or drug of choice. Dr. [redacted] interpreted this to mean that nabilone has a lesser abuse potential than marijuana. The more appropriate comparison in this case would be the delta-9-THC by the same route of administration. I do not believe that any kind of a quantitative statement can be made regarding the relative abuse liability of delta-9-THC and nabilone except that they produced similar effects.

Conclusions:

The sponsor has demonstrated that delta-9-THC produce similar psychomotor deficits at similar time points when administered by the same route of administration. Nabilone appears to have essentially to have the same abuse liability as delta-9-THC. There are no data to suggest that nabilone has a lesser potential for abuse than delta-9-THC.

Recommendations:

The sponsor should be asked to modify the Drug Abuse and Dependent section in the labeling. The suggested labeling is "Cesamet may produce subjective side effects which may be interpreted as euphoria or marijuana-like "high" at therapeutic doses." In studies in which the subjective effects of Cesamet

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were compared to delta-9-THC, Cesamet was shown to be both qualitatively and quantitatively similar to delta-9-THC.

Preclinical studies performed in both dogs and monkeys demonstrated that Cesamet was cannabinoid-like. As with delta-9-THC, tolerance develops rapidly to the pharmacological effects in both the dog and the monkey. Cross tolerance between Cesamet and delta-9-THC was demonstrated in the monkey.

The physical dependence capacity of Cesamet is unknown at this time. Patients who participated in clinical trials of up to 5 days duration evidenced no withdrawal symptomatology upon cessation of dosing.

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cc:
IND Orig
HFN-180
HFN-120
HFN-120/DCutright
HFN-120/ECTocus
HFN-120/FVocci/12/7/82
FT:dcm/12/7/82
DOC #4471B

Review and Evaluation of Pharmacology and Toxicology Data
and Clinical Data of NDA 19-577 with Reference To
Abuse Potential
Drug Abuse Staff Consulting Review

Sponsor: Lilly Research Laboratories
Indianapolis, IN 46285

Drug: Nabilone (CESAMET)

Nabilone is a hexahydrodibenzopyranone related to delta-9-THC. The structural formula is:

Nabilone differs from delta-9-THC by the 9-keto function and the dimethylheptyl side chain. The New Drug Application for nabilone is for the indication of alleviation of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer. The pharmacology and toxicology data and the clinical data have been reviewed by Drs. Contrera and Milliken, respectively. Reference will be made to their reviews of the drug to delineate the dose-effect relationships observed with nabilone in animals and man. Additionally, the "special studies" performed under the auspices of the CPDD and the human psychopharmacology data in the application will be reviewed. Recommendations will be made with respect to the appropriateness of scheduling under the Controlled Substances Act and labeling comments to be addressed in the Drug Abuse and Dependence section of the professional product labeling.

Pharmacology:

The effect of nabilone on spontaneous and schedule-controlled behavior was studied in mice, rats, cats, dogs and monkeys and rats, pigeons, monkeys, respectively. The general effect on spontaneous motor activity and the normal behavioral repertoire of the animals was CNS depression. The results of the monkey studies will be discussed in greater detail in the section reviewing special pharmacology studies. The effects of nabilone on schedule-controlled behavior were complex, variable at times, and probably both species and paradigm-specific.

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Nabilone was active in two analgesic screens, the acetic acid writhing model in mice and the tail-jerk test in rats. The effects of nabilone were not antagonized by naloxone. Additionally, the effects of morphine were not antagonized by nabilone. From these data it appears that nabilone does not produce antinociception through a direct opiate receptor mediated mechanism nor is it an opiate antagonist.

Nabilone and delta-9-THC were compared for inhibitory effects on prolactin release in rats pretreated with 5-HTP and fluoxetine. Both nabilone and delta-9-THC decreased prolactin release in 5-HTP treated rats.

Nabilone was evaluated for morphine-like activity in the non-dependent and morphine-dependent chronic spinal dog. Delta-9-THC, nabilone, and naltrexone had antinociceptive activity in the flexor and skin twitch tests. Also noted for all three drugs was hypothermia, mydriasis and behavioral calming. These effects were not antagonized by naltrexone. Delta-9-THC, nabilone, and naltrexone suppressed withdrawal signs in morphine-dependent dogs undergoing withdrawal. The results suggest some common actions between morphine and cannabinoids although there is no evidence that the cannabinoids interact with an opioid receptor mechanism.

The ability of nabilone to suppress morphine withdrawal in morphine-dependent monkeys was tested in the CPDD program. Nabilone partially suppressed the signs of retching and vomiting in the single dose substitution test in morphine-abstinent monkeys. The signs of ptosis, pupillary dilatation, ataxia and decreased responsiveness to stimulation by observers were also reported. Nabilone is not a morphine-like agonist in the dependent monkey.

Acute administration of nabilone in non-dependent monkeys resulted in ptosis, dosing, mydriasis, ataxia and a reduced responsiveness to stimulation from observers and cagemates. The constellation of drug-induced signs was scored and a dose-effect curve was determined. Nabilone was approximately 1/2 as potent as levonantradol and 5 times as potent as delta-9-THC in producing acute effects.

A chronic (30-day) administration study utilized an escalating dose regimen, starting at 0.3 mg/kg every 12 hours and finishing at a dose of 30 mg/kg every 6 hours. Tolerance developed to the acute effects. Initially, some effects could be restored by 1/4 log dose escalations; however, beyond a dose of 1.7 mg/kg (day 13), further dose increments had no effects on scored signs. Although the signs were absent, animals did not appear normal as they were often found lying prostrate on the cage floor. Doses as high as 170 mg/kg of nabilone had no effect on animals receiving 30 mg/kg/6 hrs. These monkeys also demonstrated cross-tolerance to delta-9-THC or levonantradol. There was minimal, if any, cross-tolerance to morphine.

Naloxone challenge failed to precipitate withdrawal signs. Abrupt discontinuation of nabilone also failed to elicit signs of an abstinence syndrome.

In separate studies, codeine-tolerant rhesus monkeys failed to self-administer nabilone (3.2×10^{-4} to 3.2×10^{-2} mol/kg/injection), delta-9-THC (10^{-3} to 10^{-1} mol/kg/injection), or levonantradol (doses not legible from figure).

The acute toxicity of nabilone was investigated in five species. Signs of toxicity in mice and rats were hypoactivity, limb weakness, slow respiration, hyperirritability when handled, catalepsy, hypothermia and diuresis. Mice had, in addition, straub tail and signs of ptosis. The LD₅₀ in mice was estimated to be between 1000 and 2000 mg/kg; the LD₅₀ on rats was greater than 2000 mg/kg.

Cats administered 1 mg/kg doses of nabilone, p.o., had mild ataxia and slight mydriasis which began 1 hr after dosing and persisted for 3 to 4 hours.

Dogs were administered nabilone, 1 mg/kg, p.o. in three dosage forms: (1) as a suspension in aqueous 1% tween 80 vehicle; (2) as a polyvinylpyrrolidone (PVP) co-precipitate; or (3) as a formulation of nabilone/lactose (or starch) in a 1:9 ratio. The first two formulations produced ataxic effects at two hours whereas the third formulation was without effect. Dogs given nabilone-PVP at a dose of 5 mg/kg developed mydriasis, slow pupillary responses to light, ataxia and sedation within one to three hours of dosing. Other early effects seen infrequently were myoclonus, retching, emesis, salivation, dry mouth, hyperirritability to sound, and one tonic seizure (one dog). All animals survived and presented with signs of ataxia, lethargy and slow, pupillary responses to light at 25 hours. Toxic signs resolved gradually on the second through fourth days. Dogs given single i.v. doses of nabilone (in an ethanol vehicle), 1 mg/kg, became ataxic within 10 minutes and lost consciousness for 48 hours. Upon regaining consciousness, animals were anorectic for an additional 48 hours but were normal in appearance by the fifth day of dosing.

Two rhesus monkeys (one male, one female) were administered 5 mg/kg nabilone (in a 1% tween 80 vehicle) by nasogastric intubation. The female was slightly ataxic 1-1/2 hours after dosing but was normal by 3 hours. The male was unaffected. _____ monkeys tolerated single .10 mg/kg doses of nabilone when given as the PVP co-dispersion. Animals became hypoactive and sedated within 15 to 30 minutes and remained in this condition during the first day. By day 2, the animals appeared normal.

Subchronic toxicity studies of nabilone by the intravenous and oral routes were conducted in the rat. In the 14-day i.v. study (R-374) toxic signs diminished by the fourth day, suggesting tolerance development. In the 92-day

feeding study (R-1003) nabilone was administered at doses of 6.25, 12.5 or 25 mg/kg. The high dose group was hyperirritable to touch and catatonic during the first week of the study. These signs rapidly resolved, again suggesting tolerance development to nabilone. A second feeding study in 344 rats (R-418) utilized dietary concentrations of 0.00156, 0.00625, 0.0250 or 0.1 percent nabilone which provided average daily doses of 1, 5, 19, and 93 mg/kg. Animals in the three upper dose groups exhibited hyperactivity during the first three weeks. In the 5 mg/kg group, rats remained hyperactive throughout the study whereas the upper two dose groups exhibited hypoactivity throughout the rest of the dosing period.

In the dog, the subchronic toxicity of nabilone was evaluated by oral and i.v. routes of administration. A 92-day study of oral nabilone (at 0.25, 0.5, and 1.0 mg/kg/day) in beagle dogs observed that ataxia was produced during the first week (D-4013). This effect was not noted after the second week, indicating rapid development of tolerance. A higher dose range (0.5, 1.0 and 2.0 mg/kg) was used in the second oral nabilone study (D-3558). Several effects were observed during the first three weeks of the study to which tolerance developed: hypoactivity, ataxia, anorexia, hypothermia, moderate-to-severe tear flow reduction, and conjunctival hyperemia. Mydriasis was a persistent effect during the first four months. At 7 months, cumulative toxicity caused termination of the study. Two, 6, and 7 dogs, in the low, medium and high-dose groups, respectively, had died or were sacrificed in a moribund condition. Convulsions often preceded death. Of note, gradual deterioration of the animals' conditions was not observed.

An intravenous toxicity study of nabilone utilized a fixed dose of 0.4 mg/kg (D-3374). Signs of drug effect included anorexia, hyperirritability to touch, decreased respiration, sedation, fine tremors and ataxia. All signs except anorexia, diminished between the third and fifth day of dosing. Animals were tolerant for the remainder of the study except for a transient mild ataxia occurring immediately after dosing. A five-day i.v. toxicity comparison of nabilone and its SSS-carbinol metabolite was performed in beagle dogs. (2 mg/kg, both drugs). Signs of CNS depression were noted with either drug. Plasma samples taken from dogs in both groups revealed that SSS-carbinol to nabilone ratios were 22 to 37, indicating that the SSS-carbinol had blood levels of drug about twice those found in nabilone treated dogs.

A one-year study of the toxicity of nabilone by the nasogastric route of administration in rhesus monkeys (M-6080). Three males and three females per group received either 0, 0.1, 0.5 or 2.0 mg/kg of nabilone/day; a fifth group was given 2.0 mg/kg 1 day on an intermittent basis. Sedation and hypoactivity were observed in groups dosed above 0.1 mg/kg. Single episodes of emesis and ataxia were observed in the high-dose group. Tolerance developed rapidly to the CNS effects.

Clinical studies

The abuse potential of nabilone in human psychopharmacology trials was studied by _____ et al and _____. In the study by _____ and _____ 6 healthy male volunteers who were experienced marijuana smokers were assigned 1 of 5 treatments in a 5-way crossover design. The treatments compared oral and i.v. nabilone, oral and i.v. delta-9-THC and placebo.

The study was conducted in a double-blind manner with a repeated measures design blocking over subjects. Treatment orders were randomly assigned to eliminate any order effect. The treatments were administered over a 3-week period with treatments separated by at least 3 days. Each subject received: (1) placebo orally and i.v., (2) nabilone (2 mg, p.o.) and placebo i.v.; (3) THC orally at a dose of 17.5 mg and placebo i.v., (4) placebo orally and nabilone (0.25 mg, i.v.); and (5) placebo orally and THC (2.2 mg, i.v.).

Dosages were selected for oral administration to be those commonly employed for antiemetic dosing. Intravenous doses were selected on the basis of prior information and interest in maintaining an oral/parenteral ratio of 9/1.

Subjects were monitored every 30 minutes for changes in supine and standing blood pressure for eight hours following drug administration. Pulse rate was monitored at 15-minute intervals for 4 hours and at 30-minute intervals for the remaining four hours of the test session. Subjective effects of the treatments were assessed by subjects completing a modified Cornell Medical Index (CMI) questionnaire and an Addiction Research Center Inventory (ARCI) scale every 15 minutes for the first 4 hours and every 30 minutes for the remaining 4 hours of the test session. Subjects were also observed for objective signs, and a tape recording of discussions with the subjects regarding their experience during each experimental session was made. Subjects were also asked to write a description of the effects of each experimental session. At the end of the five sessions each subject was asked to relate which treatment he preferred.

As expected, active treatments elevated standing and supine heart rates. The effects were statistically significant ($p < 0.001$) when the standing and supine heart rate means were compared using _____ new multiple range test. Delta-9-THC (i.v.) produced the greatest increase and was significant from all other treatments. Nabilone (i.v.) produced the next largest increase and was significantly different from the three remaining treatments.

Subjective assessments using the ARCI questionnaire failed to demonstrate differences in most instances. However, the _____ Medical Index was more sensitive to differences in drug effects with respect to both "total" score and a "high" subset. Differences in time-action curves and time to maximal response were also observed. Intravenous administration of delta-9-THC and nabilone achieved the highest mean responses. These effects occurred early in

the study (1-2 hours) whereas the oral formulations achieved their peak effects at 2-3 hours. A greater CMI "high" score was achieved by i.v. delta-9-THC compared to i.v. nabilone at one hour. Additionally, these two treatments differed significantly from the oral preparations and placebo.

The subjective effects of nabilone did not equal or surpass those elicited by delta-9-THC within routes of administration. However, except for the one-hour i.v. time points, these differences did not achieve statistical significance.

In terms of subject preference, the treatments were ranked THC (i.v.) nabilone (i.v.) nabilone oral THC oral placebo. All active treatments were significant from placebo ($p < 0.05$) but there were no statistically significant differences among the active treatments.

The sponsor concluded that nabilone does not appear to produce an equal degree of euphoria as delta-9-THC when compared by a similar route of administration. This conclusion is based on a single dose comparison; thus, euphorogenic potential at equipotent doses was not assessed. Therefore, differences in euphoria within routes of administration may reflect potency differences rather than differences in intrinsic activity.

The second study, conducted by Dr. _____ utilized 3 groups of marijuana smokers (occasional, intermittent, or regular) to discriminate possible differences between nabilone, delta-9-THC, and marijuana in the production of subjective effects. Subjects were also offered an operant paradigm in which to work for preferred drug or money.

A total of 24 subjects were inducted into the study. The study group was comprised of healthy adult male marijuana smokers between the ages of 21 and 30 years-old. Each subject served as his own control in a consecutive 5-day study in which the following treatments were administered: nabilone (2 mg), nabilone placebo, a standardized marijuana cigarette (1 gm containing 2% delta-9-THC), a standardized marijuana placebo cigarette, delta-9-THC capsules (17.5 mg) and delta-9-THC placebo capsules. Each subject received one active drug and two placebos on each drug day. Treatments were counterbalanced so as to control for order effects. Additionally, treatment days were color coded so that subjects could choose their preferred treatment for the operant paradigms.

Subjects discriminated active treatments from placebos. Regular users of marijuana ranked "highs" as follows: marijuana cigarette oral THC oral nabilone. Intermittent marijuana smokers expressed the same ranking order whereas occasional users reported equivalent degrees of intoxication following marijuana, THC and nabilone administration.

All regular users preferred marijuana cigarettes. All intermittent users preferred marijuana except one who preferred delta-9-THC. Five of the

occasional users selected marijuana and the other three did not work for any drug.

Dr. _____ concluded that nabilone was considerably less reinforcing than marijuana or delta-9-THC.

This study is flawed in a manner analogous to the Lemberger study. In order to make conclusions about differences in intrinsic activity, equipotent dosages should be used. As single doses of delta-9-THC, nabilone and marijuana were used, potency differences may account for differences seen among drug "high" values.

The sponsor has also analyzed results of clinical pharmacology studies with respect to the abuse potential of nabilone. "IND protocol 1" suggests that 5 mg is reliably more euphorogenic than 2.5 mg. The small number of subjects (n = 3) precluded a firm conclusion.

Results of "IND protocol #2" suggest a rapid tolerance to 2 mg, b.i.d., nabilone when the drug is administered for 7 days. Some euphoria breakthrough was noted with a dose of 5 mg. Partial loss of tolerance occurred within one week; the 5 mg dose approximately doubled the CMI score of the previous 5 mg dose. Abrupt discontinuation of a one-week regimen of 2 mg of nabilone, b.i.d., did not result in a withdrawal syndrome.

In a second study where nabilone (1 mg, b.i.d.) was administered for two weeks, 2/6 subjects initially experienced euphoria for the first days; thereafter, tolerance developed to the effect. The magnitude of tolerance development was not quantified.

An intravenous study (IND protocol #3) was conducted in eight subjects. Of five subjects who received 0.5 mg of nabilone, three of these subjects experienced euphoria, dizziness and dry mouth.

The frequency of CNS effects of nabilone in a patient population can be inferred from clinical trials data. The protocol numbers referred below may be found in the _____ review.

Protocol #20.

This multicenter protocol assessed nabilone (2 mg, every 12 hours) given for a 1 to 5 day chemotherapy cycle compared to 10 mg of prochlorperazine administered every 12 hours.

a. Dr. _____ treated 58 patients with nabilone and 53 patients with prochlorperazine. The nabilone group experienced the following incidence rates of adverse reactions: drowsiness (39.7%), vertigo (39.7%), dry mouth (27.4%) and a high feeling (19%). Other nabilone effects included asthenia,

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decrease in concentration, excessive appetite, sleep disturbance, hypotension (3/53 patients). The prochlorperazine group reported effect incidence with drowsiness (26.4%), vertigo (13.2%) and occurring with the highest rates.

b. _____ study involved 43 patients on nabilone prochlorperazine. Side effects observed in the nabilone group in 18 patients (41.9%), a high feeling in 17 (39.5%), and vertigo (34.9%). Similar reactions in the prochlorperazine group included drowsiness, a "high" feeling in 1 patient and vertigo in

c. The third part of the multicenter study was conducted. Only 10 patients were enrolled. One patient discontinued because of severe hallucinations.

Side effect results were tabulated across the three studies; the most common adverse reactions was reported by Dr. _____ page 7 of her review and is reproduced below:

<u>Adverse Reaction</u>	<u>Nabilone (111)</u>	<u>Prochlorperazine</u>
Drowsiness	43 (38.7%)	13 (17.5%)
Vertigo	41 (36.9%)	3 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.3%)	2 (1.9%)
Asthenia	10 (9.0%)	4 (3.9%)

Additionally, hallucinations were reported in 4 patients receiving

Protocol 28

This multicenter (6) study compared the antiemetic effects of a nabilone (2 mg) administered every 12 hours to placebo. Of the entered into the study, 183 patients received at least one dose of nabilone. The following side effect incidence for the nabilone-treated group:

<u>Side Effect</u>	<u>No. of patients</u>	<u>%</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.2
Ataxia	20	10.9
Depersonalization syndrome	18	9.8
Euphoria	17	9.3
Sleep Disturbance	15	8.2
Dysphoria	14	7.7

_____ noted the psychiatric effects (depersonalization syndrome, euphoria, dysphoria) were described by the study oncologist and a psychiatric consultation was not made. It was noted that patients recovered after stopping nabilone therapy.

Evaluation:

Nabilone is both chemically and pharmacologically similar to delta-9-THC. The most consistent effect of nabilone across animal species is mild CNS depression, manifested by hypoactivity and ataxia. As with delta-9-THC, tolerance development is rapid and of a large magnitude. In the dog, typical descriptions of delta-9-THC-like static ataxia are reported for nabilone. These effects fade rapidly during chronic dosing, indicating rapid tolerance development. In the monkey, nabilone produced signs of ptosis, dozing, mydriasis, ataxia and reduced responsiveness to stimulation. These signs were reproduced by administration of delta-9-THC or levonantradol, the only differences being in drug potency. A 3-log shift to the right occurred with chronic nabilone (3 weeks) dosing, indicating a high magnitude of tolerance. Cross-tolerance to delta-9-THC and levonantradol but not morphine was demonstrated.

In separate experiments, nabilone was administered to morphine-dependent monkeys undergoing withdrawal in the single dose substitution test. Partial alleviation of signs was observed. However, this cannot be interpreted to infer that nabilone has morphine-like agonist properties. Other evidence that nabilone is lacking in morphine-like properties includes lack of precipitation of withdrawal by naloxone in nabilone-treated monkeys and lack of cross tolerance to morphine.

Two human psychopharmacology studies conducted by _____ et al and _____ were reviewed. Although nabilone was found to produce less subjective effects than delta-9-THC in both studies, these conclusions were based on single dose comparisons. Thus, there is a common flaw in both studies in that a potency ratio was not established. Euphorigenic potential differences should be assessed at equipotent doses. Although the doses used may be approximately equipotent, the differences seen may reflect differences in potency rather than differences in intrinsic activity.

_____ finding that marihuana was the preferred drug among subjects in his study points out that nabilone would probably be a secondary choice as a drug of abuse. However, preference between equipotent doses of delta-9-THC and nabilone may not exist.

Other human studies evaluated by the sponsor demonstrate that supratherapeutic doses (5 mg) are more reliably euphorigenic than the proposed clinical dose of 2 mg. However, the small number of subjects in the study obviates a firm conclusion about the overlap between the clinical dose (2 mg) and the dose range which elicits subjective effects.

The review of the clinical studies of the pharmacologic properties of the 2 mg dose of nabilone noted a significant number of CNS side effects, suggesting that there is substantial overlap between the recommended clinical dose range and the subjective cannabinoid effect range.

Conclusions:

Nabilone has a high potential for abuse. It is chemically and pharmacologically similar to delta-9-THC. The sponsor has not demonstrated any differences in abuse potential between nabilone and delta-9-THC.

Recommendations:

1. If and when the new drug application for nabilone is approved or considered approvable, nabilone should be evaluated by the Drug Abuse Advisory Committee.
2. Nabilone should be recommended by the Division for control under the CSA.
3. The Division position should be that there is no actual difference in abuse potential between nabilone and delta-9-THC. Thus, nabilone should be controlled in the same schedule as that recommended for delta-9-THC (CII upon marketing approval). However, if delta-9-THC is reconsidered or scheduled in Schedule III, then nabilone should be placed in schedule III also.

Frank J. Vocci, Jr., Ph.D.
Frank J. Vocci, Jr., Ph.D.

cc:

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FJVocci/10/26/82

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Edit:FVocci/11/19/82

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**REVIEW AND EVALUATION OF CLINICAL DATA OF NDA 18-677
ORIGINAL SUBMISSION**

Date on cover letter of submission: February 16, 1982

Date Received in HFD-120: March 8, 1982

**Sponsor: Lilly Research Laboratories
Indianapolis, IN 46285**

**Name of Drug: Nabilone (Generic Name)
Cesamet (Trade Name)**

Related IND: This IND was submitted in 1974 for clinical testing as an anti-anxiety agent. Later, in 1976 phase 2 antiemetic studies were begun. The anti-anxiety studies were discontinued for lack of efficacy.

Class of Drugs: A synthetic cannabinoid for oral administration.

Sole Indication for the NDA Submission: For the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

Material Submitted: 24 volumes of which the last 2 volumes contain microfiche of individual raw data on 325 patients in a variety of nabilone studies.

Efficacy of nabilone for the control of nausea and vomiting occurring during cancer chemotherapy treatment is presented in 2 pivotal studies comparing: (1) nabilone against prochlorperazine (Protocol 20), and (2) nabilone against a placebo (Protocol 28).

Both protocols were multicenter, double-blind, randomized with crossover through 2 cycles of cancer chemotherapy. Safety was observed for use of nabilone and prochlorperazine regardless of whether the individual study was completed. After completion of 2 cycles, if the patient made the request, nabilone was re-instituted on open label and any subsequent adverse reactions were included.

The first efficacy study (Protocol 20) was performed in 3 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against prochlorperazine.

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Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg capsule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour capsule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scale. The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In addition, monitoring of vital signs and laboratory studies were performed at intervals. These additional observations were of no value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Results of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1: Vol. 10, p.93

Clinical Investigator (301)
Charles W. Young, M.D.

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Sloan-Kettering Institute
New York, New York.

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cisplatin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
<u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
<u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
<u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

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Safety Evaluation of Dr. Young's Study (Investigator 003)

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20, Vol.11, p.1

Clinical Investigator (302)
Lawrence H. Einhorn, M.D.
Indiana University Medical Center
Indianapolis, IN

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and

bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	27
Nabilone better	1
Same	8
Prochlorperazine better	
<u>Severity of Nausea</u>	21
Nabilone better	10
Same	5
Prochlorperazine better	
<u>Food Intake</u>	18
Nabilone better	11
Same	7
Prochlorperazine better	
<u>Patient Preference</u>	29
Nabilone better	1
Same	6
Prochlorperazine better	
<u>Physician's Evaluation of Efficacy</u>	26
Nabilone better	8
Same	2
Prochlorperazine better	

Safety Evaluation of Dr. Einhorn's Study (Investigator 302)

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients

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(41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

Study #3: Protocol 20, Vol.11, p.205

Clinical Investigator
Rubin Bressler, M.D.
University of Arizona School of Medicine
Tucson, Arizona

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriamycin in combination with other chemotherapeutic agents was one common denominator.

Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75) patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed to complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

Nabilone

Prochlorperazine

	<u>NABILONE</u>	<u>PROCHLORPERAZINE</u>	
Frequency of vomiting	<u>42</u>	<u>24</u>	<u>9</u>
Severity of Nausea	35	13	27
Food Intake	31	14	30
Investigator's Global Evaluation	47	9	19
Patient Preference	55	15	5

Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

<u>Adverse Reaction</u>	<u>Most Common Adverse Reactions</u>	
	<u>Nabilone (111)</u>	<u>Prochlorperazine (103)</u>
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by body systems, the greatest number occurred in the nervous and psychiatric systems with nabilone. Most of these represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55

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(62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control.

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nabilone was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1: Vol. 11, p. 335

Clinical Investigator (001)
Stephen E. Jones, M.D.
Professor of Medicine
University of Arizona Health Sciences Center
Tucson, Arizona

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of

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chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytosan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
 <u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
 <u>Food Intake</u>	
Nabilone better	3
Same	7
Placebo better	1
 <u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
 <u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of Dr. Jone's Study - Investigator (001):

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

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Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety: Dr. Jones - The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

Study #2: Vol. 12, p. 14

Clinical Investigator (002)
Lawrence H. Elhorn, M.D.
Associate Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4
<u>Severity of Nausea</u>	

Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1
<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation: Dr. Einhorn's Study (002)

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

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Conclusions on Safety: Dr. Einhorn (002)

A very large majority 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

Study #3: Vol.12, p.227

Clinical Investigator (003)
Frank A. Greco, M.D.
Assistant Professor of Medicine
Vanderbilt University Hospital
Nashville, Tennessee.

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4: Vol.12, p.307

Clinical Investigator (004)
John R. Durant, M.D.
Director, Comprehensive Cancer Center
University of Alabama
Birmingham, Alabama

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol

deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5: Vol.13, p.12

Clinical Investigator (005)
Martin Levitt, M.D.
Manitoba Cancer Treatment and Research Foundation
University of Manitoba
Winnipeg, Canada

This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 3 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19

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Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	1
Same	3
Placebo better	32

Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

Adverse Reactions: Dr. Levitt's Study (005)

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both

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nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6: Vol.13, p.210

Clinical Investigator (006)
John C. Gunnell, M.D.
Glendale Hematology and Oncology Medical Group
Glendale, California

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	23
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2

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Same	5
Placebo better	25

Efficacy Conclusions

This group of Dr. Gunnell's patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions - Dr. Gunnell's Study

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%) experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)
Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	9 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #621 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo)

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in

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their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
Jones	11
Einhorn	33
Greco	5
Durant	8
Levitt	36
Gunnell	36
TOTAL	129

Efficacy results are combined in the following comparison in similar manner to the individual studies.

	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32
Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99(77%)	15(12%)	15(12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3

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Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Epilogue

Two submissions to _____ were received since submission of NDA 18-677 on 2/17/82.

- 1) Date of submission 2/23/82. Received in Drug Abuse Staff 4/14/82. Included 2 F1639s on death's of patients. Both patients were in Protocol #28 (nabilone-placebo). Both had extensive carcinoma and died of their disease. Deaths were not drug related.
- 2) Date of submission 3/22/82 consisting of annual report. Reviewed by Drug Abuse Staff on 4/12/82. Report of 1 death attributed to lung carcinoma. This patient was in the placebo cycle and had not received nabilone.

Conclusions:

Nabilone is approvable for efficacy on the basis of clinical review. Nabilone was found to be superior to both prochlorperazine and placebo in the control of nausea and vomiting occurring in patients undergoing cancer chemotherapy.

Safety has to be evaluated on a risk vs benefit result. Adverse reactions

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were much higher in the nabilone treated group cycles. The most common adverse reactions in descending order were drowsiness, vertigo, dry mouth, and alteration of mood. After completion of the study, a large majority (75%) of patients chose nabilone for future chemotherapy cycles.

Before final approval is given for nabilone, the following recommendations are made:

1. Consultation with HFD-150, Division of Oncology and Radiopharmaceutical Drug Products in regard to:
 - a. Concurrence with appropriateness of the chemotherapy schedules with patients disease as selected by the sponsor. Do these patient's illnesses and treatment comprise the usual caseload of an oncologist?
 - b. Concurrence with oncologist's experience with prochlorperazine with dosage and times of administration.
 - c. Assistance with labeling of package insert.
2. Consultation with Drug Abuse Staff in regard to drug abuse potential. This will include scheduling the drug.
3. Confirmation of statistical analysis of study by the Division of Biometry.

Margaret A. Milliken

Margaret A. Milliken, M.D.
Medical Officer, HFD-120

cc:

Orig: NDA 18-677

HFD-120

HFD-180

HFD-120/FVoccl

HFD-120/MMilliken/EBarker

rd/mb/8/25/82/FT/8/31/82/DOC 3554B

E. Barker

CESAMET - Lilly
NDA 18-677

V. Medical Summary Basis of Approval:

A. Introduction:

Nabilone "Cesamet" is a synthetic cannabinoid for oral use. It is supplied as 1.0 mg capsules. The sole indication for its use is severe nausea and vomiting occurring in patients receiving cancer chemotherapy.

B. Adequate and Well Controlled Studies:

The sponsor submitted 2 multicenter studies.

The first multicenter study (Protocol #20) was performed at 3 hospital centers, comparing Nabilone against a known antiemetic, namely, prochlorperazine. The results of these studies will be designated Protocol #20.

The second adequate and well controlled study (Protocol #28) was performed at 6 medical centers in which antiemetic results were compared with patients receiving placebo while undergoing cancer chemotherapy.

Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg capsule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour capsule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scale. The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In

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addition, monitoring of vital signs and laboratory studies were performed at intervals. These additional observations were of no value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Results of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1: Vol. 10, p. 93

Clinical Investigator (301)
Charles W. Young, M.D.
Sloan-Kettering Institute
New York, New York.

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cisplatin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic

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drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
<u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
<u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
<u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

Safety Evaluation of Dr. Young's Study (Investigator 003)

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients

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with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20, Vol. II, p. 1

Clinical Investigator (302)
Lawrence H. Einhorn, M.D.
Indiana University Medical Center
Indianapolis, IN

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	27
Same	1
Prochlorperazine better	8
<u>Severity of Nausea</u>	
Nabilone better	21
Same	10
Prochlorperazine better	5
<u>Food Intake</u>	
Nabilone better	18

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Same	11
Prochlorperazine better	7
<u>Patient Preference</u>	
Nabilone better	29
Same	1
Prochlorperazine better	6
<u>Physician's Evaluation of Efficacy</u>	
Nabilone better	26
Same	8
Prochlorperazine better	2

Safety Evaluation of Dr. Einhorn's Study (Investigator 302)

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients (41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

Study #3: Protocol 20, Vol.11, p.205

Clinical Investigator
Rubin Bressler, M.D.
University of Arizona School of Medicine
Tucson, Arizona

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriomycin in combination with other chemotherapeutic agents was one common demoninator.

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Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75)-patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

	Nabilone		Prochlorperazine	
	Better	Same	Better	Same
Frequency of vomiting	42	9	24	9
Severity of Nausea	35	27	13	27
Food Intake	31	30	14	30
Investigator's Global Evaluation	47	19	9	19
Patient Preference	55	5	15	5

Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

Adverse Reaction	Most Common Adverse Reactions	
	Nabilone (111)	Prochlorperazine (103)
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by systems, the greatest number occurred in the nervous and psychiatric systems with nabilone. Most of these

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represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

- A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55 (62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nabilone was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity

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of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1: Vol.11, p.335

Clinical Investigator (001)
 Stephen E. Jones, M.D.
 Professor of Medicine
 University of Arizona Health Sciences Center
 Tucson, Arizona

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytosan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
<u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
<u>Food Intake</u>	
Nabilone better	3

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Same	7
Placebo better	1
<u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
<u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of Dr. Jone's Study - Investigator (001):

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety: Dr. Jones - The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

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Study #2: Vol.12, p.14

Clinical Investigator (002)
Lawrence H. Einhorn, M.D.
Associate Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1
<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and

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cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation: Dr. Einhorn's Study (002)

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

Conclusions on Safety: Dr. Einhorn (002)

A very large majority 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

Study #3: Vol.12, p.227

Clinical Investigator (003)
Frank A. Greco, M.D.
Assistant Professor of Medicine
Vanderbilt University Hospital
Nashville, Tennessee

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one

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dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4: Vol.12, p.307

Clinical Investigator (004)
John R. Durant, M.D.
Director, Comprehensive Cancer Center
University of Alabama
Birmingham, Alabama

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5: Vol.13, p.12

Clinical Investigator (005)
Martin Levitt, M.D.
Manitoba Cancer Treatment and Research Foundation
University of Manitoba
Winnipeg, Canada

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This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 3 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19
Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	1
Same	3
Placebo better	32

Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

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Adverse Reactions: Dr. Levitt's Study (005)

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6: Vol.13, p.210

Clinical Investigator (006)
John C. Gunnell, M.D.
Glendale Hematology and Oncology Medical Group
Glendale, California

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

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	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	23
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2
Same	5
Placebo better	25

Efficacy Conclusions

This group of Dr. Gunnell's patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions - Dr. Gunnell's Study

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%) experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)

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Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	9 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #621 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo:

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
Jones	11
Einhorn	33
Greco	5
Durant	8
Levitt	36
Gunnell	36
TOTAL	129

Efficacy results are combined in the following comparison in similar manner to the individual studies.

	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32

Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99(77%)	15(12%)	15(12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3
Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

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Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Margaret A. Milliken

Margaret A. Milliken, M.D.

mb/1/27/83
DOC #4883

Medical Officer Consultation on NDA 18-677

NDA: 18-677

Applicant: Eli Lilly and Company

7 1982

Name of Drug: Generic Nabilone
Trade Cesamet

Dose Form and Route: 1 mg pulvules for oral administration.

Proposed Indication: For control of nausea and vomiting due to cancer drugs.

Clinical Evaluation:

Efficacy is demonstrated in two pivotal studies of double blind, randomized prospective crossover design. One study compares nabilone with the standard antiemetic prochlorperazine and the other study compares nabilone with placebo. Nabilone toxicity is quite significant.

Comments and Recommendations:

1. The prochlorperazine dose is at the low end of the range generally used.
2. A complete response category (no nausea or vomiting) would be helpful. However, the parameters used are (in toto) adequate.
3. Cancer chemotherapy drugs may not all produce vomiting by the same mechanism. An antiemetic effective for one cancer drug may not be effective for all others. In addition some cancer drugs cause severe vomiting and others little if any. The approval of metoclopramide (Reglan) is restricted to nausea and vomiting due to cis platin. In the THC NDA applicant showed results of TIC with each of several chemotherapy regimens.

It is probably not feasible to test each antiemetic with all existing anticancer drugs and certainly not with all combinations of these drugs in use. Applicant has studied nabilone with a reasonably representative spectrum of cancer drugs with emphasis on those causing the most severe nausea and vomiting. However, the results should be broken down into separate categories according to the cancer drug given with emphasis on those cancer drugs known to cause the most severe vomiting. The following categories are suggested: cis platin based regimens, non cis platin based regimens, DTIC based regimens without cis platin, adriamycin based regimens without cis platin or DTIC, Cytosan based regimens without adriamycin, DTIC or cis platin and any regimen occurring with sufficient frequency to make evaluation meaningful. We should not require nabilone to be

effective in each of these subcategories of the .05 level of significance, but one wants to see at least a favorable trend in all or most categories if labeling indicates efficacy for all cancer chemotherapy drugs.

4. Package Insert:

- (a) Cancer patients often have impaired liver function. There may be need for reduced dose in these patients as there is for THC. Both are excreted via the bile.
- (b) In the PRECAUTIONS, GENERAL section "tranquilizers and sedatives" should be added at the end of the first sentence.
- (c) The PATIENT INFORMATION section should indicate the patient should be accompanied by a responsible adult who can do any driving and remain with the patient for 24 hours after drug administration or until all drug side effects have subsided. This would be consistent with THC labeling.
- (d) Is there any indication of tolerance with nabilone?
- (e) The proposed schedule (first dose the night before) appears different than that used in the well controlled trials.

John R. Johnson M.D.
John R. Johnson, M.D.
11/22/82

cc: Orig, NDA 18-677
HFN-150
HFN-150/Div File
HFN-220
HFN-150/Johnson
HFN-150/Ripper/Behrens
F/T by P. Amoss/11/24/82
Wang #0003B

*Wang
11/24/82*

AUG 2 1983

Second Review and Evaluation of
Clinical Data of NDA 18-677

Data on Cover Letter of Submission: February 16, 1983

Data of Completion of Second Review: July 27, 1983

Medical Officer's First Review Completed: August 31, 1982 and approved by
Acting Group Leader, Dr. Eileen Barker

Medical Officer's Second Review: Refer to Memo of Division Director dated
July 5, 1983 (attachment)

Sponsor: Lilly Research Labs
Indianapolis, Indiana

Name of Drug: Nabilone (generic)
Cesamet (trade)

Related IND/NDAs: }

This IND was submitted in 1974 for clinical testing as an anxiety agent. In 1976, phase II antiemetic studies were begun. The antianxiety studies were discontinued for lack of efficacy.

Class of Drugs: A synthetic cannabinoid for oral administration

Sole Indication for the NDA Submission: For the control of nausea and vomiting caused by chemotherapeutic agents in the treatment of cancer

Material Submitted: 24 volumes of which 2 volumes contain microfiche of raw individual data on 325 patients. In addition since submission on February 6, 1982, the sponsor has submitted follow-ups in 3 volumes which include Canadian, French, English and Netherland's experience with adverse reactions.

Review of Cesamet for Efficacy and Safety

Phase I, Protocol 1, performed by Dr. Lemberger at the Lilly Laboratory in Indianapolis.

This was a single dose ranging study using 3 human male volunteer prisoners. Dosage range of nabilone varied from 0.1 mg to 5.0 mg. Conclusion of investigator was that nabilone in doses less than 3 mg produced no effect. Nabilone at 3 mg. produced euphoria, dry mouth. At dosage at 5 mg, subjects experienced postural hypotension, dry mouth, and euphoria.

Conclusion Phase I, Protocol 1: Continue testing limiting top dosage to 5 mg/per day.

Phase I, Protocol 2: Effects of multiple doses of nabilone in 3 human male volunteers

Dosage was 2 mg three times daily for 7 days

Each subject experienced nausea, dizziness, drowsiness and blurred vision

Postural hypotension was evident in each of the subjects

Protocol 7 - early phase II dose ranging study - Part I

Clinical Investigators - Rubin Bressler, et. al., University of Arizona, School of Medicine, Tucson, Arizona

Protocol 7, Part I is the first clinical study of dose ranging in 13 cancer patients who had experienced nausea and vomiting during chemotherapy and who were resistant to prochlorperazine. This was an open study with pregnancy being the only excluding factor.

Nabilone dosage was given three times daily ranging from 1 mg three times daily as compared with 2 mg three times daily. Nabilone was given 30m minutes before start of intravenous cancer chemotherapy.

Monitoring consisted of observation, BP every four hours, recording patient's statements and a complete battery of blood studies before and after drug usage.

Results were inconclusive. Most patients felt partial improvement under each dosage. None received complete relief. There were no serious adverse reactions; the recorded observations are quite similar to the phase I studies; namely drowsiness, dry mouth, and dizziness. Mild hypotension was observed in only 1 patient on the lower dose of nabilone (1 mg t.i.d.)

Conclusion: 13 patients who had received no relief from previous cycles of prochlorperazine experienced some improvement on 2 dosage ranges of nabilone.

Protocol 7, Part II (See Protocol #20, Study 2 on page 7)

Protocol 9, Vol. 9 p.9: This was a late phase II study, testing nabilone at 1 mg or 2 mg with comparison with prochlorperazine at 5 mg and 10 mg. Purpose was to standardize a dosage schedule and protocols before starting phase III studies.

Investigator: Lawrence Einhorn, M.D.
Indiana University, School of Medicine

Ninety-eight (98) patients entered the study of which 83 patients completed two cross over cycles. Most of these patients (75) received cisplatin for testicular or ovarian cancer.

Final dosage form was determined at completion of the study using all 96 patients who were eligible to evaluate dosage level although only 83 were considered candidates for efficacy evaluation. The following doses were selected:

	Daily Dose	No. of Patients
Nabilone	less than 2.0 mg	10
	2 mg to 4 mg	35
	4 mg or more	51
		<u>95</u>

The discrepancy in total numbers is that some patients never finished the cross over or broke protocol for other reasons.

Dosage conclusion for future phase III studies

Nabilone - 2 mg every 12 hours

Prochlorperazine 10 mg every 12 hours

Efficacy value was based on (1) frequency of vomits, (2) severity of vomits, (3) and food intake using rating of: (1) None = 0, (2) Mild = 1, (3) moderate = 2 and (4) severe = 4.

Clinical comparison of efficacy observation:

Clinical comparison of efficacy observation:

Frequency of vomits	Number of patients
Nabilone better	62
Same	7
Prochlorperazine better	14
	<u>83</u>

Severity of Nausea

Nabilone better	52
Same	15
Prochlorperazine	14
	<u>81</u>

Food Intake

Nabilone better	40
Same	30
Prochlorperazine	11
	<u>81</u>

Safety Observations

The largest number of patients treated with nabilone experienced both Central Nervous System and Psychiatric Manifestation Drowsiness in 84 patients receiving nabilone as compared with 80 patients with prochlorperazine; vertigo in 72 nabilone patients compared with 36 patients on nabilone.

The next largest adverse experiences were a "high" feeling observed in 44 patients on nabilone although 7 patients receiving prochlorperazine reported a "high" feeling.

Ortho-static hypotension was observed in 3 patients on nabilone.

Conclusions: Protocol 9 was valuable in determining protocols in phase III studies. From this experience, the 2 pivotal studies were developed as a double-blind cross-over, comparing the efficacy and safety of nabilone to either prochlorperazine or placebo. Moreover, the dosages were determined as were the conduct and analysis of major testing.

Phase III studies are designed to observe the efficacy of Cesamet in control of nausea and vomiting to cancer chemotherapy when compared against compazine (Protocol #20) and against placebo. Review of these studies follow.

Basic Protocol 20 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy which must be identical protocols. Each patient must have had nausea and vomiting on at least 2 previous cancer treatment cycles. One test drug was a 2 mg capsule of nabilone to be administered every 12 hours while cancer treatment was being received until it was completed in a 1 to 5 day cycle. Nabilone therapy was started 1 hour before initiation of cancer treatment. The comparison drug was 10 mg spansule of prochlorperazine in a special capsule resembling the nabilone capsule. It was administered every 12 hours until cancer cycle was completed. To obtain full benefit of the 12 hour spansule, this drug was also given the night before treatment. For the nabilone group, a placebo capsule was administered the night before treatment.

Evaluation was made by a blinded investigator noting the frequency of vomits, the severity of nausea, and comparison of food intake during treatment days determined by a simple rating scales.

Rating scales were the following:

<u>Nausea</u>	<u>Food Intake</u>	<u>Global Impressions</u>
0 = none	0 = none	1 = very good
1 = mild	1 = less than usual	2 = good
2 = moderate	2 = usual amount	3 = fair
3 = severe	3 = more than usual	4 = poor
		5 = very poor

Regarding vomiting scales: The patient had to have at least 2 less vomiting episodes on Day 1. To achieve a rating of better, the number of vomiting spells had to be at least 50% less than the corresponding cross-over study.

The investigator also noted his global impression of efficacy and the patient was permitted to state which antiemetic treatment, if any, he wished to continue for future cancer treatment cycles. Also, to be eligible for efficacy evaluation, the patient must have completed at least one day of antiemetic - cancer chemotherapy on each of 2 complete cycles. In this way, he would have received both antiemetic test drugs. In addition, monitoring of vital signs which included postural hypotension of lying and standing blood pressure and pulse rate at 2 hours after receiving medication and laboratory studies were performed at intervals. These laboratory studies consisted of hematology, urinalysis, SMA-12 to be done prior to use of each study drug. These additional observations were of little value because the patient was already ill from cancer, and was compounded by receiving chemotherapy. No EKGs were routinely made. Moreover, in questioning for adverse reactions each patient was asked if he had experienced a "high feeling." The patient simply answered "yes" or "no" with no description. This question was asked only in comparison of nabilone to prochlorperazine (Protocol 20). The patient was not specifically asked whether he felt "high" in the larger study comparing nabilone to placebo in Protocol #28 to follow.

A patient was considered ineligible for evaluation in the study if, 1) a second antiemetic drug was used other than the study drugs, including marijuana, 2) study drug was not administered concomitantly with chemotherapy, 3) a change in cancer chemotherapy between two cycles of treatment, and 4) failure to complete the crossover.

Performance of Protocol #20

A comparison of efficacy of nabilone with prochlorperazine. This study was performed in 3 medical centers.

Study #1: Vol. 10, p. 93

Clinical Investigator (301)
Charles W. Young, M.D.
Sloan-Kettering Institute
New York, New York

Sixty-seven (67) patients entered the study but ultimately only 32 patients were considered evaluable by having completed the crossover through 2 cycles of cancer chemotherapy. All 35 dropouts were accountable as having incomplete crossover, protocol deviation, or were suspended from study in 1979 while the dog problems in pharmacology were being resolved.

The most common cancer chemotherapy for the 32 evaluable patients was cis-platin in combination with other cancer drugs. Twenty-one (21) patients received this treatment. The remaining 11 patients received miscellaneous groups of drugs in a cyclic manner. The majority of patients were receiving treatment for cancer of lung, bladder and testicle.

Efficacy evaluation was based on 32 patients who completed 2 cycles, whereas safety evaluation was made on all patients who entered the study for nabilone. For statistical analysis, many factors were considered such as matching patients with drug cycles, number of days in cycle, patients observations, observer's observation.

A rough comparison by the investigator and by the patients of the 2 antiemetic drugs is presented.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	11
Same	6
Prochlorperazine better	15
<u>Severity of Nausea</u>	
Nabilone better	12
Same	17
Prochlorperazine better	3
<u>Food Intake</u>	
Nabilone better	10
Same	16
Prochlorperazine	6
<u>Preference of Patients</u>	
Nabilone better	18
Same	7
Prochlorperazine better	7

From a clinical view, nabilone reduced the severity of the nausea but not the number of vomits. Patient preference was greater for nabilone.

Safety Evaluation of Dr. Young's Study (Investigator 003)

A total of 58 patients who started the study received nabilone and 53 patients also received prochlorperazine. These numbers include the completed

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crossovers, the terminations, the open label continued study and the suspension of clinical studies during 1979. Statistical analysis will provide a clearer comparison, but a larger number of nabilone patients experienced more severe reactions than the prochlorperazine group.

Of the 58 nabilone patients, 47 or 81% were observed to have one or more adverse reactions. Drowsiness 39.7%, vertigo 39.7%, dry mouth 22.4% and a "high feeling" in 19% were the largest groups noted in the nabilone patients.

Comparing the 53 patients who received prochlorperazine, 27 (50.9%) noted at least one adverse reaction. Drowsiness was the largest adverse reaction noted by 14 patients or 26.4%. Next was vertigo in 7 patients (13.2%), dry mouth in 2 (3.8%).

Other adverse reactions noted in the nabilone group were asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache, hypotension. An even smaller number of patients in the prochlorperazine group noted similar reactions. Hypotension was expressly monitored and occurred in 3 patients with nabilone and 1 patient with prochlorperazine.

One death occurred in a 35 year old man with lung cancer and bone metastases who had completed one cycle with nabilone twenty-two days before death and was awaiting the prochlorperazine cycle. No autopsy was done. The ADR (1639) states he died of cancer of lung with metastases to bone. Reviewer's comment: This death was not related to nabilone.

Study #2: Protocol 20, Vol.11, p.1

Clinical Investigator (202)
Lawrence H. Einhorn, M.D.
Indiana University Medical Center
Indianapolis, IN

The study was begun with 49 patients but only 36 patients completed 2 complete cycles of cancer chemotherapy with at least one complete day of nabilone. Thirteen (13) patients failed to complete 2 cycles of crossover, or other protocol violations leaving a total of 36 evaluable patients.

Of the 36 evaluable patients the most common cancer chemotherapy was cisplatin usually in combination with bleomycin and vinblastine. This particular group of drugs was used in the 23 patients (64%) while other combinations without cisplatin were used in the remaining 13 patients (36%). All the cisplatin patients had testicular cancer. The remainder were composed of breast and bladder cancer and lymphomas.

Efficacy evaluation was based on the 36 patients who completed 2 cycles of treatment with the crossover but the safety evaluation was made on all who

entered the study for nabilone or chose to continue afterward on open-label nabilone.

A rough comparison for efficacy has been made on comparison of antiemetic cycles by the observations of patient and investigator.

<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	27
Same	1
Prochlorperazine better	8
 <u>Severity of Nausea</u>	
Nabilone better	21
Same	10
Prochlorperazine better	5
 <u>Food Intake</u>	
Nabilone better	18
Same	11
Prochlorperazine better	7
 <u>Patient Preference</u>	
Nabilone better	29
Same	1
Prochlorperazine better	6
 <u>Physician's Evaluation of Efficacy</u>	
Nabilone better	26
Same	8
Prochlorperazine better	2

Safety Evaluation of Dr. Einhorn's Study (Investigator 302)

Of the 49 patients who entered the study, there were 43 patients who entered the study who received nabilone and 42 patients who received at least one dose of prochlorperazine. These numbers include the completed crossovers (36), protocol violations, continuing open-label study after completion.

In the group of 43 patients receiving nabilone, 34 (79.1%) reported at least one adverse reaction, whereas, in the prochlorperazine group of 42 patients, only 15 (35.7%) reported at least one adverse reaction.

The common adverse reactions were nabilone were drowsiness in 18 patients (41.9%), a "high" feeling in 17 (39.5%), vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 (2.4%) and vertigo in 1 (2.4%) patient. Curiously 4 patients on nabilone experienced dry mouth compared to 0 patients on prochlorperazine.

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Study #3: Protocol 20, Vol. 11, p. 205

Clinical Investigator
 Rubin Brassler, M.D.
 University of Arizona School of Medicine
 Tucson, Arizona

Study #3 had relatively few patients enrolled because of the temporary suspension of clinical testing in 1979, for evaluation of toxicity in dogs. It was subsequently never resumed nor enlarged.

A total of 10 patients entered the study of which 7 patients completed 2 cycles of test drug with cancer chemotherapy. This group had no lung or testicular cancer; nor was cisplatin the primary chemotherapeutic agent. The group of 7 patients is too small to list the cancers; however, adriamycin in combination with other chemotherapeutic agents was one common demoninator.

Efficacy is not evaluated because of the small number of patients. Three of the completed 7 patients asked to continue nabilone on the open-label option.

Concerning safety, it was necessary to discontinue nabilone during Day 1 of treatment because of severe hallucinations with 1 patient. This small study group while on nabilone experienced drowsiness and vertigo similar to the larger studies.

Composite Results of Protocol #20 (Comparing Nabilone with Prochlorperazine):

A total of 126 cancer patients were studied by 3 investigators in which a double-blind crossover study compared the antiemetic results of nabilone with prochlorperazine through 2 cycles of chemotherapy.

Seventy-five (75) patients completed 2 cycles of treatment with at least one day of treatment with nabilone or prochlorperazine. Fifty-one (51) patients were not evaluable because 14 had protocol deviations and 37 failed to complete 2 cycles required for crossover evaluation.

Five factors considered for efficacy were, 1) frequency of vomits, 2) severity of nausea, 3) food intake, 4) investigators global impression, and 5) patients preference for future treatment cycles.

	<u>Nabilone</u>	<u>Prochlorperazine</u>	
	<u>Better</u>	<u>Better</u>	<u>Same</u>
Frequency of vomiting	42	24	6
Severity of Nausea	35	13	27
Food Intake	31	14	30
Investigator's Global Evaluation	47	9	19
Patient Preference	55	15	5

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Adverse Reactions - Comparison between nabilone and prochlorperazine: All 126 patients were evaluated: 111 patients received at least 1 dose of nabilone and 103 received at least 1 dose of prochlorperazine.

Adverse Reaction	Most Common Adverse Reactions	
	Nabilone (111)	Prochlorperazine (103)
Drowsiness	43 (38.7%)	18 (17.5%)
Vertigo	41 (36.9%)	8 (7.8%)
"High" Feeling	29 (26.1%)	4 (3.9%)
Dry Mouth	18 (16.2%)	2 (1.9%)
Asthemia	10 (9.0%)	4 (3.9%)

Adverse Reactions: When compared by body systems, the greatest number occurred in the nervous and psychiatric system with nabilone. Most of these represented drowsiness, vertigo, and "high" feeling. However, hallucinations were reported in 4 patients with nabilone, 0 with prochlorperazine. The "high" feeling occurred in 30 with nabilone and 4 patients with prochlorperazine. When these individual reports are checked against individual microfiche reports, these adverse reactions ceased with stopping therapy.

Conclusions:

Protocol #20 - Comparing results of nabilone against those of prochlorperazine.

Of a total of 126 cancer patients, 75 were evaluable under Protocol #20. Nabilone was numerically superior to prochlorperazine in reducing the frequency of vomiting, severity of nausea and possibly decreasing anorexia.

A much higher incidence of adverse reactions occurred with use of nabilone than with prochlorperazine. Drowsiness, vertigo, a "high" feeling and dry mouth were much more common with nabilone. These reactions included the entire group. Hallucinations occurred in 4 nabilone patients. One patient died of his cancer three weeks after nabilone treatment.

Of the 75 completed patients, 55 (73.3%) elected to continue nabilone under an open-label for future chemotherapy cycles.

The 3 clinical investigators rating of benefits to individual patients was 55 (62%) for nabilone, 15 (20%) for prochlorperazine and 5 (7.7%) showed no difference.

Protocol #28

The second efficacy study (Protocol 28) was performed in 6 medical centers for the purpose of controlling nausea and vomiting resulting from cancer chemotherapy by comparing the outcome of using nabilone against a placebo control

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11

Basic Protocol #28 is a double-blind, randomized crossover for 2 treatment cycles of cancer chemotherapy comparing the efficacy of a fixed dose of nabilone against placebo control. This protocol is similar to Protocol #20 in design except for using a placebo instead of prochlorperazine. Nabilone was administered as a 2 mg capsule q 12 h while the patient is receiving cancer treatment, usually 1 to 5 days. The first dose is administered the night before and then given 1 to 3 hours before starting chemotherapy on the first day. It is given at 12 hours thereafter.

Efficacy was determined in a similar manner to the study comparison with prochlorperazine. Observation was made of the frequency of vomits, severity of nausea, and comparison of food intake. At the end, the observer made a global rating for each cycle of treatment, and each patient expressed his preference for antiemetic. To be eligible for efficacy evaluation, a patient must have completed at least one day of treatment for each of two consecutive chemotherapy cycles.

Safety was monitored by observation, by laboratory tests, and blood pressure checks. All patients in the study were included in safety report, whereas, the efficacy study was limited to completed patients.

Results of Protocol #28

A comparison of efficacy of nabilone with placebo. This study was conducted in 6 Medical Centers.

Study #1: Vol. 11, p. 335

Clinical Investigator (001)
Stephen E. Jones, M.D.
Professor of Medicine
University of Arizona Health Sciences Center
Tucson, Arizona

Twenty-four (24) cancer patients entered the study resulting in 11 evaluable patients who had completed the study through 2 consecutive cycles of chemotherapy. The 13 dropout patients were accounted for as protocol deviations on incomplete crossovers. The most common cancer chemotherapy for the 11 evaluable patients was a combination of Adriamycin, Cytoxan, and Vincristine. This study had only 3 patients receiving cisplatin with other drug combinations perhaps reflecting a larger number of patients with lymphomas.

The following efficacy comparisons by the investigator and the completed patient of nabilone to placebo is presented:

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<u>Frequency of Vomits</u>	<u>Number of Patients</u>
Nabilone better	7
Same	1
Placebo better	3
<u>Severity of Nausea</u>	
Nabilone better	6
Same	4
Placebo better	1
<u>Food Intake</u>	
Nabilone better	3
Same	7
Placebo better	1
<u>Patient Preference</u>	
Nabilone better	6
Same	1
Placebo better	4
<u>Adverse Experiences</u>	
Nabilone better	1
Same	1
Placebo better	9

Efficacy Conclusions:

With only 11 evaluable patients with varying cancer diagnosis and type of chemotherapy, no valid conclusions can be drawn. Improvement in the frequency of vomits and severity of nausea appears to favor nabilone over placebo. The patients preference was nabilone.

Safety Evaluation of Dr. Jones' Study - Investigator (001):

Of the 24 cancer patients who entered the study, 22 patients received at least 1 dose of nabilone and 21 received at least 1 dose of placebo.

Adverse Reactions to Nabilone - Of the 22 patients who received at least 1 dose of nabilone, 18 (82%) experienced at least 1 adverse reaction. The common ones are listed.

<u>Adverse Reaction</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	16	73%
Vertigo	15	68%
Hypotension	3	14%
Nausea	3	14%
Dry Mouth	3	14%

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Convulsions occurred in one of this nabilone treated group 2 days after a 5 day treatment cycle. The patient had advanced testicular cancer and received cisplatin with other cancer drugs. He was re-hospitalized but no cause was found for the convulsions.

Conclusions on Safety. Dr. Jones - The large majority of patients experienced drowsiness (73%) and vertigo (68%).

Seven of the 22 patients (32%) elected to continue on open-label nabilone as their preference.

Study #2: Vol.12, p.14

Clinical Investigator (002)
Lawrence H. Einhorn, M.D.
Associate Professor of Medicine
Indiana University Medical Center
Indianapolis, Indiana

Forty-two (42) patients entered in this study resulting in 33 evaluable patients who had completed 2 consecutive cycles of cancer chemotherapy. The 9 uncompleted patients are accounted for. The most common cancer was testicular (45%) and breast (33%) cancer. The use of cisplatin and other chemotherapy combinations parallels these diagnoses. Leukemia and lymphoma were minority diagnoses in this study so far.

The following efficacy comparison by the investigator and the completed patients (33) of nabilone to placebo is presented:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	8
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	27
Same	7
Placebo better	5
<u>Food Intake</u>	
Nabilone better	13
Same	15
Placebo better	5
<u>Physicians Evaluation</u>	
Nabilone better	27
Same	5
Placebo better	1

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<u>Adverse Experiences</u>	
Nabilone better	0
Same	1
Placebo better	32

Efficacy Conclusions:

This is a more homogenous group of cancer patients in regard to diagnosis and cancer chemotherapy. Also, this study included a larger group of completed patients (33) as compared with the previous study of 11 completed patients. However, results were the same. A decrease in the frequency of vomits and the severity of nausea was found in the nabilone group. Patients preference of 30 (91%) was for nabilone.

Safety Evaluation: Dr. Einhorn's Study (002)

All 42 patients entering this study received at least one dose of nabilone; of these patients, 41 experienced at least 1 adverse reaction to nabilone.

The common adverse reactions are listed:

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Drowsiness	36 (86%)
Dry Mouth	23 (55%)
Vertigo	21 (50%)
Ataxia	15 (36%)
Sleep disturbance	10 (24%)
Headache	9 (21%)

Two patients died in this study after completing nabilone cycle and before beginning placebo cycle. Patient #213 died 2 weeks after receiving nabilone and patient #214 died 6 weeks after nabilone treatment.

Conclusions on Safety: Dr. Einhorn (002)

A very large majority 86% of nabilone treated patients experienced drowsiness. The next most common reactions were dry mouth in 55% and vertigo in 50%. These are acceptable adverse reactions.

Twenty-two (22) patients chose to continue with open-label nabilone after completion of the study.

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Study #3: Vol.12, p.227

Clinical Investigator (003)
Frank A. Greco, M.D.
Assistant Professor of Medicine
Vanderbilt University Hospital
Nashville, Tennessee

Fourteen (14) patients entered this study but only 5 fulfilled the protocol requirements to be considered evaluable.

The number of evaluable patients (5) is too small to be considered for efficacy rating. A total 11 patients of the 14 starters received at least one dose of nabilone. However, of this small group of 11 patients, 6 patients chose to continue future treatment with open-label nabilone.

Adverse Reactions

Dry mouth, vertigo, and drowsiness occurred in over 50% of the 11 nabilone patients which is consistent with experience. One patient was dropped from the study after one 2 mg nabilone because of hallucinations necessitating deferring chemotherapy for 1 day. The patient recovered.

Conclusions

None. Study is too small, but is in agreement with previous studies.

Study #4: Vol.12, p.307

Clinical Investigator (004)
John R. Durant, M.D.
Director, Comprehensive Cancer Center
University of Alabama
Birmingham, Alabama

This study was also a small one. Sixteen (16) patients entered the study, resulting in 8 patients evaluable for efficacy of the dropouts, 6 were for incomplete crossover, 1 for change in chemotherapy, and 1 for protocol deviation.

Efficacy should not be evaluated in this total of 8 eligible patients because of its small number of subjects.

Adverse Reactions

All 16 patients received at least one dose of nabilone; the most common reactions were vertigo in 11 patients (69%), dry mouth in 7 (44%), sleep disturbance in 7 (44%), drowsiness in 4 (25%), and asthenia in 2 (13%).

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Five patients elected to continue future cycles of cancer treatment on open-label nabilone.

Study #5: Vol.13, p.12

Clinical Investigator (005)
 Martin Levitt, M.D.
 Manitoba Cancer Treatment and Research Foundation
 University of Manitoba
 Winnipeg, Canada

This was the largest single study using Protocol #28 (placebo controlled, double-blind, crossover). Fifty-eight (58) cancer patients entered the study resulting in 36 patients completing 2 cycles of cancer chemotherapy, hence evaluable patients. Most dropouts were due to incomplete crossovers. The majority of the patients had lung, ovarian, and breast cancers. Of the 36 evaluable patients, 12 received cisplatin with combinations of other cancer drugs, while 24 patients received combined chemotherapy without cisplatin. There were only 2 lymphomas in 58 patients.

The following efficacy comparisons of nabilone to placebo are made by the investigator and the patient:

	<u>Number of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	29
Same	3
Placebo better	4
<u>Severity of Nausea</u>	
Nabilone better	26
Same	8
Placebo better	2
<u>Food Intake</u>	
Nabilone better	19
Same	12
Placebo better	5
<u>Patient Preference</u>	
Nabilone	28
Same	5
Placebo better	3
<u>Physicians Global Impression Concerning Adverse Reactions</u>	
Nabilone better	7
Same	3
Placebo better	32

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Efficacy Conclusions:

This is the largest single group of evaluable patients (36), thus far. Efficacy of nabilone to placebo was clearly established. The nabilone group had a decrease in the frequency of vomiting and severity of nausea. Food intake was inconclusive. Patients preferred nabilone 28 to 8 over placebo. Finally, 11 patients chose to continue future therapy cycles with open-label nabilone.

Adverse Reactions: Dr. Levitt's Study (005)

Of the 58 patients entering this study, 51 patients received at least one dose of nabilone and 46 patients received at least one placebo dose. Forty-seven (47) of the 51 patients who received nabilone experienced at least one adverse reaction. Again, the adverse reactions were predominantly neurological and psychiatric. A listing of the most frequent adverse reactions is presented.

<u>Adverse Reaction</u>	<u>No. of Patients</u>
Vertigo	34 (67%)
Drowsiness	31 (61%)
Depersonalization	18 (35%)
Dry mouth	12 (24%)
Disorientation	8 (16%)

Comment on Adverse Reactions

This study is different from the other studies in having so many depersonalization syndromes. On looking at individual microfiche patient records, there is no real description of symptoms; only the diagnosis appears. To judge the severity, one patient elected open-label nabilone despite the depersonalization experience and proceeded through 7 cycles of chemotherapy each resulting in depersonalization syndrome with each cycle. Another patient was described as having depersonalization syndrome with both nabilone and placebo. The other Cancer Centers in Protocol #28 reported this condition so infrequently that a possible conclusion lies in lack of psychiatric experience on the part of the attending oncologist. Nevertheless, the higher percentage of psychiatric adverse reactions has to be noted.

Study #6: Vol.13, p.210Clinical Investigator (006)

John C. Gunnell, M.D.
Glendale Hematology and Oncology Medical Group
Glendale, California

Forty-five (45) cancer patients entered this study resulting in 36 patients considered evaluable by completing cycles of cancer chemotherapy. Dropouts are accounted for. Breast and lung carcinomas accounted for one-half of the

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cancer diagnoses. The other half were spread along many miscellaneous diagnoses. In this study group only 8 patients received cisplatin in combination with other cancer drugs; whereas, 28 patients received cancer drugs in a variety of single and combination administration.

The following efficacy comparisons of nabilone to placebo were made by the investigator and the patient.

	<u>No. of Patients</u>
<u>Frequency of Vomits</u>	
Nabilone better	20
Same	5
Placebo better	11
<u>Severity of Nausea</u>	
Nabilone better	23
Same	9
Placebo better	4
<u>Food Intake</u>	
Nabilone better	12
Same	21
Placebo better	3
<u>Physician's Global Impression of Efficacy</u>	
Nabilone better	25
Same	5
Placebo better	6
<u>Adverse Reactions</u>	
Nabilone better	2
Same	5
Placebo better	25

Efficacy Conclusions

This group of Dr. Gunnell's patients also had 36 evaluable patients as did the Study #5, just preceding this review. Both the frequency of vomiting and the severity of nausea were reduced with nabilone. Many more adverse reactions were noted with nabilone. (See below). When patients were questioned about their preference of antiemetic for future chemotherapy, 25 (69%) of the 36 preferred nabilone.

Adverse Reactions - Dr. Gunnell's Study

Forty-one (41) of the total patients who started the study received at least one dose of nabilone. Of this group of 41 patients, thirty-two (32 or 78%)

experienced at least one drug related adverse reaction. These adverse reactions were similar to other studies and are tabulated as follows:

<u>Adverse Reactions</u>	<u>No. of Patients</u>
Vertigo	22 (54%)
Drowsiness	18 (44%)
Dry Mouth	15 (37%)
Euphoria	11 (27%)
Dysphoria	9 (22%)

Comment on Adverse Reactions

Studies #5 and #6 have both recorded higher psychiatric symptoms; otherwise, both studies conform to previous observations. Checking individual case reports on microfiche in regard to euphoria and dysphoria (Study #6), these are diagnoses with no descriptions. It is not clear that any psychiatrist was consulted. One patient #521 completed a 5 day cycle with nabilone plus chemotherapy. She had far advanced metastatic disease of breast. She died 6 days after last dose of nabilone. Her death was attributed to cancer. This patient is recorded on microfiche to have excellent results with nabilone during the treatment period.

Composite Results of Protocol #28 - (Comparison of Nabilone with Placebo):

A total of 199 patients were studied by 6 clinical investigators in which a double-blind crossover study compared the antiemetic effects of nabilone with placebo through 2 identical courses of cancer chemotherapy.

Of these 199 patients, 129 completed 2 cycles of chemotherapy and had received at least one dose of nabilone. These 129 patients were reviewed for safety and efficacy. The unevaluable patients numbering 199 are accounted for in their individual reviews. The most common cause of dropouts was failure to complete 2 identical chemotherapy cycles for cancer.

A comparison of nabilone to placebo is made by pooling the 129 evaluable patients contributed by 6 clinical investigators.

<u>Investigator</u>	<u>Evaluable Patients</u>
Jones	11
Einhorn	33
Greco	5
Durant	8
Levitt	36
Gunnell	36
TOTAL	129

Efficacy results are combined in the following comparison in similar manner to the individual studies.

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	<u>Nabilone Better</u>	<u>Placebo Better</u>	<u>Same</u>
Frequency of Vomiting	98	13	18
Severity of Nausea	85	12	32
Food Intake	53	14	62
Investigator's Global Impression of Efficacy	98	13	18
Patient Preference	99 (77%)	15 (12%)	15 (12%)

Composite of Adverse Reactions Occurring in Protocol #28 - (Nabilone vs Placebo)

Of the 199 patients entering the multicenter study 183 patients received at least 1 dose of nabilone.

Most common adverse reactions (over 10% incidence):

<u>Adverse Reactions</u>	<u>No. of Patients</u>	<u>Percent</u>
Vertigo	102	55.7
Drowsiness	96	52.5
Dry Mouth	57	31.1
Ataxia	20	10.9

Psychiatric reactions occurring mostly in the 2 largest studies (#5 and #6) accounting for a total of 72 patients are represented as:

Depersonalization Syndrome	18	9.8
Euphoria	17	9.3
Sleep Disturbance	16	8.7
Dysphoria	14	7.7

There is no description of these reactions or indication that these diagnoses were made by a psychiatrist. All patients appear to have recovered when nabilone was terminated.

Conclusions: Protocol #28 (Nabilone-Placebo)

Of a total of 199 patients studied in 6 Medical Centers, 129 were evaluable through 2 cycles of cancer chemotherapy. Nabilone was numerically superior in reducing the frequency of vomiting and the severity of nausea. Improvement in anorexia was less remarkable.

Incidence of adverse reactions was high in the nabilone group. Over 50% showed vertigo and drowsiness. Dry mouth occurred in 30%. These reactions are of no major concern considering the fact that the patient is being treated

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for cancer with a variety and a combination of cancer chemotherapy. Psychiatric manifestations occurred in just under 10% of these patients. There was no uniformity or description of these diagnoses. Patients appear to have recovered upon stopping the drug.

Of the 129 completed study patients, ninety-nine (99 or 77%) elected to continue under open-label nabilone for future cycles of cancer chemotherapy.

Comments on Consultations:

Statistics were reviewed by Dr. Nevius. I discussed his review with him on June 15, 1983. Protocols 7 and 9 were done as early as phase I and II to establish dosage and safety guidelines. Three of the 4 studies (protocols 9, 20 and 28) produced statistical evidence of efficacy.

Oncology consultation was reviewed on November 24, 1982 by Dr. Johnson in HFN-150, Division of Oncological and Radiopharmaceutical Drugs. I discussed with him on July 18, 1983 the variety of cancer chemotherapeutic regimens that had been treated with Cesamet. As in his memo, he felt that drugs such as Cesamet should be used in patients receiving drugs known to cause severe n and v such as cis-platin. Further, there appear to be sufficient patients that received cis-platin with Cesamet to limit the labeling at this moment for use with cis-platin only. "Reglan" (metaclopramide) still has limited use to cisplatin only. Dr. Johnson re-stated that the mechanism of nausea and vomiting may not be the same for the various carcinogenics.

Epilogue

Two submissions to _____ were received since submission of NDA 18-677 on 2/17/82.

- 1) Date of submission 2/23/82. Received in Drug Abuse Staff 4/14/82. Included 2 F1639s on death's of patients. Both patients were in Protocol #28 (nabilone-placebo). Both had extensive carcinoma and died of their disease. Deaths were not drug related.
- 2) Date of submission 3/22/82 consisting of annual report. Reviewed by Drug Abuse Staff on 4/12/82. Report of 1 death attributed to lung carcinoma. This patient was in the placebo cycle and had not received nabilone.

Conclusions and Recommendations:

In view of Dr. Leber's memo to me dated July 7, 1983, I pass on making recommendations to Dr. Leber.

Margaret A. Milliken
Margaret A. Milliken, M.D.
Medical Officer, HFN-120

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Attachment:

cc:

Orig. NDA 18-677
HFN-120
HFN-180
HFN-120/FVocci
HFN-120/Milliken/EBarker
FT/IScott/7/29/83
Doc. 7109B

Memorandum to File
NDA 18-677
(Cesamet, nabilone)
July 5, 1983

Subject: NDA 18-677 review package submitted by Dr. Milliken for supervisory review.

Attention: Dr. Milliken

The single most important review of an NDA, the review which is expected to integrate the views of each reviewing discipline into a cohesive whole, is the Medical Officer's Review. Your review of NDA 18-677, (i.e., an undated review of some 19 pages, and the 1 page addendum to it of June 27, 1983), not only fails to meet this goal, but fails to meet standards for a review focused only upon the clinical data submitted.

Consequently, your review and its associated documents (i.e., draft labeling, SBA, draft letter, etc.) are inadequate to support your recommendation that the product be approved.

The NDA review package suffers from the following defects:

1. The Medical Officer's Review describes only two so-called "pivotal" studies, Protocols 20 and 28. Other studies submitted to the NDA are not described. For example, Protocol 7 and Protocol 9, each described in the review by the statistical consultant, are not even mentioned in the Medical Officer's Review. Moreover, the Medical Officer's Review does not enumerate, in any place, the extent and type of data submitted by the sponsor. Official FDA BD Staff Manual Guide policy makes clear that an enumeration and review of all studies is required. This includes both clinical pharmacology (Phase I and Phase II) and safety data from any and all clinical studies including clinical studies to assess the product as an anxiolytic (i.e., the 1974 submission).
2. The studies that are the subject of the Medical Officer's review are described with inadequate detail.

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- a. The review fails to describe the protocol used in either of the two 'pivotal' multicenter studies in adequate detail. For example, it fails to state whether the cross-over design employed was counter-balanced. This design takes into account the order of treatment administration and is an essential feature of any adequate and well-controlled crossover study.
 - b. The review fails to describe the rating devices used in a manner that would allow anyone reading the review to understand how they were employed or what they measured.
 - c. The review of data is limited to conclusion about global efficacy for each of two treatment cycles. There is no review of the actual data on which these conclusions are based. For example, the observed difference in vomiting under the treatments compared is not presented in quantitative terms. Neither a severity of nausea, food intake and preference of patients.
3. The organization of the data elements reviewed and the plan of the review does not follow the suggestions of the consult review received from HFN-150. Dr. Johnson suggested specifically that several categories of anti-tumor chemotherapy be evaluated to determine whether or not Cesamet's alleged anti-nauseant activity was general or limited to specific types of chemotherapy (e.g., see 2nd paragraph, item 3, of the consult review, dated 11/22/82).
 4. The two protocols reviewed by the medical officer (i.e., No. 20 and No. 28), are inconsistently and inadequately evaluated.

In Protocol 20, the items reviewed for efficacy in each of the three sub-studies are not the same. In Study No. 1, by Dr. Charles Young, the outcome of four items is examined, while in Study No. 2., by Lawrence H. Einhorn, five outcome measures are examined. The results of Study No. 3 under protocol 20, by Reuben Bressler, M.D., are not enumerated at all.

Failure to enumerate the results of the last study make it difficult to interpret the accuracy of the composite data presented.

A similar problem affects protocol No. 28 and its description. Six rating categories are used to assess efficacy; however, in each of the six sub-studies, different items from this group of six efficacy variables are tabulated. Consequently, it is impossible to tell from the data representing the composite of the six studies which trials contributed which results.

5. There is a lack of internal consistency in the review concerning the outcome of events in each study. In particular, in Study No. 28, the number of individuals (i.e. 13) in which placebo was better than Cesamet,

as tabled by Dr. Milliken on page 17, is five fewer than the number obtained by adding together the number of individuals from the four individually tabled sub-studies in study No. 28 (2 studies were not individually tabled). Clearly, this is not logically possible and represents an error. There are other examples of this sort of failure to check tabled data. On page 7 of the Medical Officer's Review, the tabulated number of patients evaluated for patient preference is 75. Of these, 55 are said to have liked nabilone better than the comparison treatment. However, in the first segment of this study, 18 patients preferred nabilone, in the second, 29; thus, two studies contributing 47 subjects to this rating category.

For the Table to be correct, 8 subjects would have had to prefer nabilone in the Bressler study. However, the Bressler study only had 7 patients who were considered evaluable. On page 14 in describing the Levitt study, the text and table for the same item, patient preference, contradict one another. This lack of internal consistency raises concerns about the reliability and accuracy of the review.

5. The Medical Officer's Review fails to enumerate and evaluate basic data that bears on the safety of the product. There is no assessment of vital signs, blood pressure or laboratory data. Admittedly, one might expect great variation among the patients given their wide variety of cancers and treatments. Nevertheless, each patient's response under treatment can be compared with his own baseline rating and any differences observed can be compared among the treatments.
7. The Medical Officer's Review fails to assess the effect of dropouts on the study. While the biometric review did attempt an analysis, the Medical Officer's Review makes no comments about this issue. Obviously, the first period of a counter-balanced crossover design can be used as a parallel study. It is important to assess the outcome of all patients who received at least one treatment to see whether or not their response contradicts any conclusion regarding the efficacy of nabilone that is based solely upon subjects who completed the trial.
8. The omissions and errors in the Medical Officer's Review are carried over into the draft Summary Basis of Approval. Indeed, the medical sections of this document are little more than a direct restatement of the incomplete Medical Officer's Review.
9. The labeling review and the modification to the indications section suggested by the Medical Officer are not justified in the review. It is not evident what reason the medical officer has for restricting the Indication for nabilone use as an anti-nauseant to patients "who do not receive relief from the use of standard antiemetic drugs."

The labeling also fails to include any mention of the pharmacologist's view (given in the SBA) that the evaluation of the safety and efficacy of nabilone only allows for its short-term use in cancer patients. This caution is not given in the labeling.

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Conclusion:

The evaluation package, especially the Medical Officer's Review, is not adequate to support the approval of this drug product. A conscientious and systematic effort must be made to (1) display the data fully, (2) make certain that the data is accurate, (3) ascertain the nature of the rating scales and the variables actually rated (i.e., actual counts of vomiting episodes and severity of nausea, rather than better and worse categorizations), (4) assess the outcome using all participants in the two pivotal studies (20 and 28) who had at least one full treatment cycle on any anti-nauseant, and (5) most important of all, carry out a full safety evaluation (i.e. vital signs, BP, laboratory) supported by full statistical review. The latter is especially important, as there is a suggestion that this drug product produces hypotension, and possibly tachycardia. We must examine the effects of nabilone on blood pressure, EKG, and standard laboratory tests. In short, a much more thorough and full analysis of the data of this application is essential before we consider it ready for supervisory review.

Recommendations:

1 - The Medical Officer is to undertake immediately to correct the deficiencies enumerated in this memorandum.

2 - The completed medical review should be considered as the Medical Officer's first priority, and must be completed by July 30, 1983.

cc:
 NDA Orig.
 HFN-120
 Dr. Leber
 Dr. Barker
 HFN-120/PLeber/7/5/83
 FT/dcm/7/5/83/ft/-/7/5/83/ft/IScott/7/28/83
 Doc. 6816B

Signed P. Leber (MAM)

7/5/83

REVIEW AND EVALUATION OF CLINICAL DATA
SAFETY REVIEW

NDA 18-677

Sponsor: Eli Lilly and Co.

Drug: Generic: Nabilone
Trade ; Cesamet

Chemical: (+)-Trans-3-(1,1-dimethylheptyl)6,6a,7,8,10,Ha-
hexahydro-1-hydroxy-6,6-dimethyl-9-H-dibenzo[b,d]
pyran-9-one

Category: Cannabinoid

Indication: Control of nausea and vomiting caused by chemotherapeutic
agents used in the treatment of cancer.

Route of Administration: 1 mg and 2 mg pulvules for oral administration.

Submission Date: February 16, 1984

This submission consisted of 25 volumes and case reports submitted on microfiche. The original studies testing the drug for a variety of indications including metabolic studies, antianxiety, and glaucoma are included in the safety reviews. The major studies for antiemetic effect in cancer chemotherapy consists primarily of multicenter trials 20 and 28 and prochlorperazine controlled trials 7 and 9. These studies are also included in the safety review and are discussed first.

Background:

Nabilone is an orally absorbed synthetic cannabinoid with CNS effects similar to 9-tetrahydrocannabinol (9THC). It was originally hoped to have less toxicity and has been tested as an antianxiety agent. The present NDA would limit its use to the nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

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The original formulation was poorly bioavailable and to overcome this difficulty a new process (ethanol dissolved drug mixed with polyvinylpyrrolidone (PVP)) was used to produce 3 formulations for which a comparative bioavailability study was performed. This was subsequently deemed inadequate (Hebb - Biopharm. Rev. 5/22/83) but it is of note that in the clinical studies to be reviewed different formulations were used.

Pharmacology:

1. Antiemetic Effects:

(a) In cats BCNU produced vomiting in 50% of animals with a latency of 145 minutes (10-20 mg/kg) After pretreatment with Nabilone it failed to elicit vomiting in any of 14 trials.

(b) In cats mechlorethamine elicited prompt vomiting with 15 minutes latency in all animals. Following Nabilone it produced vomiting 2 of 8 trials after latency of 209 minutes.

(c) Nabilone did not block apomorphine emesis in the dog.

2. Effects on vomiting induced by cisplatin in pigeons: Nabilone was 80-160 times more potent than prochlorperazine (?species specific).

3. Nabilone effect on spontaneous motor activity and general behaviour was assessed in mouse, rat, cat, dog and rhesus monkey. The general effect across species was depression of motor activity and depression of normal behaviour suggesting that a sedative effect would be observed in humans.

Preliminary tests showed that Nabilone was active in analgesic tests but was not antagonized by Naloxone. In morphine-dependent monkeys undergoing withdrawal Nabilone suppressed retching and vomiting but not other signs of abstinence (mydriasis). Therefore it was considered non-opiate like.

Nabilone produced ptosis, dozing, mydriasis, ataxia and reduced responsiveness and was more potent than 9THC but in a 30 day test increasing tolerance to behavioural effects were noted. Cross-tolerance with 9THC but not with morphine was demonstrated.

In the dog static ataxia test Nabilone produced ataxia and body sway at 32 mg/kg. Two metabolites were tested and also produced ataxia the RRS metabolite more than the SSS metabolite. Brain concentrations of the SSS Carbinol can concentrate in the brain in dogs. This may account for the species specific high toxicity in dogs.

Human Studies:

Several studies were conducted in humans to elucidate pharmacology, pharmacokinetics and metabolism. Although few patients were involved in each study the side effect data were included in summary with data from other studies. They will be included in our summary.

SAFETY ANALYSISIntroduction:

Nabilone was originally thought to be less toxic than 9 THC and was introduced in humans for a number of indications including its use in glaucoma and as an antianxiety agent. The sponsor, however, decided because of toxicity to limit the indication for use of Nabilone to treatment of the emesis accompanying cancer.

A number of studies were begun which were interrupted during the study. However, safety data on all the patients who received Nabilone is included. Toxicity was striking in all studies and adverse experiences with a 5% or greater incidence is listed.

Individual studies are described below and the location of the data is indicated.

For all studies the modified Cornell Medical Index (Vol. 1.9, Appendix III, p.467) was used for scoring side effects in all patients.

A summary of adverse experiences with a 5% or greater incidence is listed on p.359.

**ADVERSE EXPERIENCES OCCURRING WITH A 5% OR GREATER INCIDENCE
DURING THE CROSSOVER-STUDIES AND DURING OPEN-LABEL STUDIES
(Drug-Related and Unknown Drug Relationship)**

Adverse Experience	Total Pts. No. of Patients	436 Percent
Drowsiness	285	65.4
Vertigo	267	61.2
Salivary Secretion Disturbance (Dry Mouth)	125	28.7
High*	116	26.6
Ataxia	55	12.6
Depression	44	10.1
Concentration Decreased	42	9.6
Vision Disturbance	39	8.9
Headache	37	8.5
Sleep Disturbance	32	7.3
Euphoria	30	6.9
Asthenia	29	6.7
Depersonalization Syndrome	28	6.4
Hypotension, Orthostatic	23	5.3

*The term "high" is not precisely defined. In the crossover studies using prochlorperazine as a control drug (269 patients), the patients were asked on a daily questionnaire if they were "high". At the same time, in 2 of these

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studies (Investigators 201 and 203) patients were asked if they were sad or "low". Without further clarification to the patients in the prochlorperazine-controlled studies, it is not possible to accurately assess the percent incidence of a marijuana-like high or euphoria. In the placebo-controlled studies (199 patients), these questions were not asked. The percent incidence of a high in these latter studies was 2.2, while the percent incidence of euphoria was 9.8.

The most important studies were multicenter protocol 20 (prochlorperazine controlled) and protocol 28 (placebo controlled). These protocols are analyzed first. The additional protocols 7 and 9 which were also prochlorperazine controlled are then reviewed. The safety data from these 4 studies has been summarized and the combined studies have been reviewed.

Following these studies the remainder of the small studies or incomplete studies are then reviewed for safety. Although individual studies were often small the description of side effects in these early studies is comprehensive.

In all these studies a Modified Cornell Medical Index (Vol. 1.9, Appendix III, p.467) was used for scoring side effects in all patients.

3 formulations of Nabilone have been used:

- I. One was prepared by a rotary evaporation procedure. Most of the clinical work was performed with this formulation.
- II. Another was prepared by a granulation procedure. Some of the work in the later stages utilized this formulation.
- III. A third was a formulation of Nabilone in starch. I and II utilized Nabilone and PVP co-precipitate. In III Nabilone alone was placed in a starch formulation. These 3 formulations were considered bioequivalent (see review).

Human studies to be reviewed first consist of the two pivotal multicenter studies:

1. Protocol 20 - Cesamet with prochlorperazine as active control. (Studies 7 and 9 are also prochlorperazine controlled and will be reviewed subsequently).
2. Protocol 28 - Placebo controlled.

Protocol 20:

- Vol. 1.10 - Young (301) pg. 93 - Sloan Kettering
 Vol. 1.11 - Einhorn (302) pg. 1 - Indiana University
 Vol. 1.11 - Bessler (306) pg. 205 - University of Arizona
 Vol. 1.10 - Composite Study, pg. 8

NDA 18-677

Title: A Study of the Antiemetic Effectiveness of Nabilone.

This is a double-blind, randomized crossover study. Drugs were given in two consecutive cycles of cancer chemotherapy.

	<u>Cycle 1</u> Day	<u>Washout</u>	<u>Cycle 2</u> Day
Sequence Group I	1,2,3,4,5 Nabilone	3-6 weeks	1,2,3,4,5 prochlorperazine
Sequence Group II	prochlorperazine	3-6 weeks	Nabilone

The study drug was administered concomitantly with the chemotherapy which was administered over a period of 1 to 5 days. (See Protocol).

Young Study 301:

For the first study (Young) chemotherapy was administered for 1 to 2 days only. The test drug was generally extended to one day thereafter.

Of 55 patients who received Nabilone day 1, 40 or 73% received it on day 2. Of 52 patients who received prochlorperazine on day 1, 39 (75%) received the drug on day 2.

Most intense cancer chemotherapy generally was administered on day 1.

Drug doses were Nabilone (Cesamet) 2 mg bid and prochlorperazine 10 mg bid. Not all patients received the total calculated dose on each day.

FREQUENCY OF PATIENTS BY TOTAL DAILY DOSE

	<u>DAY</u>						
	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Nabilone							
2 mg	51	16	10	3	1	1	1
4 mg	1	39	30	0	0	0	0
Greater than 4 mg	-	-	-	-	-	-	-
TOTAL	52	55	40	3	1	1	1

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6

Prochlorperazine					
10 mg	48	14	8	1	1
20 mg	2	38	31	1	1
30 mg	-	-	-	-	-
Greater than 30 mg	-	-	-	-	-
TOTAL	50	52	39	2	2

Only patients in whom it was anticipated that the cancer chemotherapy would remain the same during the two consecutive cycles, and who had experienced nausea and vomiting during at least two previous cycles of chemotherapy were admitted to the study. A variety of diagnoses and cancer chemotherapy were permitted in the study. Generally multiple drugs were most common on day 1. The study results were reported separately for two groups, those who received Cisplatin with other combinations and those who received other combinations without Cisplatin. Patients were also divided by high ($> 100 \text{ mg/M}^2$) and low ($< 100 \text{ mg/M}^2$) of Cisplatin.

However, adverse experiences or side effects were not reported separately by either of these criteria. These are reported only related to the drug administered (Nabilone or prochlorperazine).

Safety evaluation was based on the following:

1. Vital Signs - Specifically the relationship of recumbent and standing blood pressures at baseline and 2 hours following each drug dose.
2. Patient daily report of adverse effects in questionnaire (e.g., Modified Cornell Medical Index (Vol. 1.9, Appendix III)). At the end of the study the investigator recorded an impression of the relationship of each adverse effect to the study drug.
3. Laboratory studies performed prior to the study between the cycles prior to cycle 2.

Statistical Evaluation of the adverse effects was limited to numbers of patients experiencing each effect and a summary of those adverse experiences with a 5% or greater incidence. No risk/benefit calculation was made. Adverse experiences were analyzed by the magnitude of the daily dose (less 2.0 mg Nabilone or $> 2.0 \text{ mg}$ Nabilone, $< 10 \text{ mg}$ prochlorperazine or $> 10 \text{ mg}$ prochlorperazine). Adverse experiences during open-label administration of Nabilone in those patients who elected to continue one drug were also reported although open-label administration was terminated.

67 patients entered the study, 43 males, 24 females ages 18-77. The most common chemotherapy was Cisplatin in combination with vincristine for lung, bladder and testicular cancer. 10 patients chose to continue open-label Nabilone.

The most common adverse experiences were drowsiness, vertigo, dry mouth and "high".

The adverse effects are reported on a total of 58 patients. These 58 patients presumably are those who received at least one dose of Nabilone on one cycle of the study.

The number of adverse experiences were apparently not related to dose for Nabilone but were dose related for prochlorperazine.

Study Drug	Average* Daily Dose	No. of Patients In Group	Drug Related	Patients Reporting At Least One Adverse Experience	
				Unknown	Drug Related Or Unknown
Nabilone	Less than 2.0 mg	14	9 (64.3%)	5 (35.7%)	13 (92.9%)
	2.01-4.0 mg	41	22 (53.7%)	12 (29.3%)	31 (75.6%)
	Unknown	3	2 (66.7%)	1 (33.3%)	3 (100.0%)
Total		58	33	18	47
Prochl.	Less than 10 mg	3	2 (15.4%)	3 (23.1%)	5 (38.5%)
	10.01-20 mg	40	9 (22.5%)	16 (40.0%)	22 (55.0%)
Total		53	11	19	27

Patient and investigator evaluations at the conclusion of the crossover study included patient overall preference between the two treatments and the investigator's global impressions, grading of severity of response by the following grading system and an assessment as to whether drug-related or unknown.

Adverse Experience:

Grading:

(1) None

(2) Did not significantly interfere with patients functioning.

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(3) Significantly interfered with patient's functioning.

(4) Outweighed the therapeutic effect.

The latter would be some comment on risk/benefit ratio although not based on statistical data.

Dropouts:

I. Reasons for Early Termination.

28 patients were terminated early.

Of these, 3 were clearly drug related and occurred on Nabilone and two were due to adverse experiences of unknown cause.

1. Case 09 - Following one 2 mg dose of Nabilone experienced dysphoria, dizziness, nausea and decreased ability to concentrate.
2. Case 28 - Cycle II of crossover, single 2 mg dose. Experienced hallucinations, somnolence, dyspnea, dizziness, numbness, confusion and visual distortions.
3. Case 36 - Single 2 mg dose. Cycle I did not like the "high" experienced and discontinued no drug.

Two questionably drug related were:

1. Case 14 - One 2 mg dose of Nabilone followed by a discovered drop-in WBC and chemotherapy was postponed. Patient also had chills, weakness, restlessness and insomnia, dizziness and hypotension. Removed from study by the investigator.

Comment: This may well represent severe ADR to drug.

2. Case 52 - Prochlorperazine day prior to chemotherapy. Following the 10 mg dose on the second day he reported dizziness, "high" and loss of equilibrium. He did not return for initiation of chemotherapy.

Comment: It is clear that some patients anticipated a "high" and their discontinuation of the drug was related to this. Whether this also affected the blind is unknown but the prochlorperazine case (#52) makes it unlikely that patients were always sure of what constituted an appropriate "high" or a side effect.

3 patients dropped out for lack of efficacy on Nabilone and 3 on prochlorperazine.

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II.

- a) 58 patients received at least one dose of Nabilone.
- b) 10 chose to continue Nabilone on an open label basis.
- c) Of the 67 randomized patients 58 received at least one dose of Nabilone and 53 received at least one dose of prochlorperazine and adverse experiences are analyzed in these patients.
- d) No correlation was made between high dose Cisplatin, low dose Cisplatin and no Cisplatin regarding ADR's. However, of the evaluable (32) patients the investigator's global impression of ADR's is as follows:

	High Dose Cisplatin	Low Dose Cisplatin	None	Combined	
				C	NC
Nabilone better	- 2	3	1	5	1
Same	- 8	2	3	10	3
Compazine better	- 3	3	7	6	7

- e) 33 of 58 patients (56.9%) who received Nabilone reported at least one drug related experience, 11 of 54 patients (20.8%) on compazine reported at least one ADR.

LION

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Drug Related and Unknown Drug Relationship)

<u>Body System</u>	<u>NABILONE</u> (Total Patients 58)		<u>PROCHLORPERAZINE</u> (Total Patients 53)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	4	6.9	2	3.8
Eye and Ear	2	3.4	3	5.7
Gastrointestinal	14	24.1	3	5.7
Metabolic and Endocrine	1	1.7	0	-
Miscellaneous	11	19.0	10	18.9
Nervous System	38	65.5	19	35.8
Psychiatric	17	29.3	6	11.3
Respiratory	1	1.7	0	-
Skin and Appendages	0	-	1	1.9

A COMPARISON OF ADVERSE EXPERIENCES WITH A 5% OR GREATER
INCIDENCE ON EITHER THE NABILONE OR PROCHLORPERAZINE CYCLE

(Drug Related and Unknown Drug Relationship)

<u>Adverse Experience</u>	<u>NABILONE</u> (58 Patients)		<u>PROCHLORPERAZINE</u> (53 Patients)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	23	39.7	14	26.4
Vertigo	23	39.7	7	13.2
Salivary Secretion				
Disturbances (Dry Mouth)	13	22.4	2	3.8
High (Euphoria)	11	19.0	2	3.8
Asthenia	5	8.6	2	3.8
Concentration Decrease	5	8.6	0	-
Excessive Appetite	5	8.6	0	-
Sedated	5	8.6	2	3.8
Sleep Disturbance	5	8.6	3	5.7
Headache	1	1.7	3	5.7
Hypotension	3	5.2	1	1.9

Table 3 gives the rank order of those ADR's occurring with a frequency of 5% or greater. It is clear that on all listings nervous system symptoms are most common and that ADR's were much more common with Nabilone. As in early studies single doses of 2 mg were accompanied by significant incidence of side effects.

In every category ADR's from Nabilone exceeded those from Compazine.

Conclusion

In this 2 day chemotherapy trial with one group of high-dose Cisplatin adverse reactions were most common in the central nervous system and were far more common with Nabilone than with control (compazine). The incidence of patients with at least one side effect was 56.9%. Single 2 mg doses were associated with side effects and led to 3 - possibly 4 dropouts.

- (1) "BP was obtained erect and recumbent in each hospitalized patient approximately 2 hours after each dose of medication and also as outpatients if they remained in the treatment setting."

There were many patients on which BP was not obtained and few in whom a full complement was obtained.

Data was available in 24 patients and "missing" in 16 to a total of 40 patients. It is not clear how this is selected from the 58 patients evaluated for safety.

Where available Nabilone showed a decrease in systolic pressure 14 patients vs. an increase in 9. A decrease occurred in 5 and an increase in 18 on prochlorperazine. The diastolic was affected in the same direction but with less striking difference (increase) in the Compazine treated group for both erect and recumbent pressures (Vol. 1.10, pg. 285-286).

No data regarding changes in laboratory data is given; however, review of patient values showed no significant deviations.

Protocol 20

Investigator: 302 Einhorn (Vol. 1.11, pg. 1)

This was the identical protocol.

49 patients (39 males and 10 females) enrolled in the crossover. 32 of the patients had testicular cancer which was usually treated with 5 days of Cisplatin with bleomycin and vinblastine generally administered concomitantly on day 1. Adverse reactions by incidence and by body system (Table 4) were similar to those found by investigator 301 despite the fact Cisplatin and other chemotherapy was only given for 2 days in 301 rather than 5 as in 302.

Incidence is based on 43 total patients (vs. 36 evaluable patients).

No distinction was made by the investigator between drug related and non-drug related experiences: both are listed together.

79.1% of Mabilone treated patients vs. 35.7% of Compazine treated patients reported at least one adverse experience.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Unknown Drug Relationship)

<u>Body System</u>	<u>NABILONE</u> (Total Patients 43)		<u>PROCHLORPERAZINE</u> (Total Patients 42)	
	<u>No. of Patients</u>	<u>Percent</u>	<u>No. of Patients</u>	<u>Percent</u>
Cardiovascular	3	7.0	0	7.1
Eye and Ear	3	7.0	3	7.1
Gastrointestinal	5	11.6	3	7.1
Genito-Urinary	1	2.3	1	2.4
Miscellaneous	13	30.2	8	19.0
Musculoskeletal	2	4.7	6	14.3
Nervous System	30	69.8	4	9.5
Psychiatric	19	44.2	2	4.8
Respiratory	3	7.0	2	4.8

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Early Terminations (Dropouts)

45 -Only one patient clearly terminated as a result of adverse experience. She received 2 days of Nabilone treatment and complained of dizziness, dry mouth, blurred vision, depression urgency, anxiety, ataxia and photophobia.

Two other patients on Nabilone experienced adverse effects which led to failure to complete Cycle 2.

#46 received Nabilone 8 mg for 5 days. He complained of a "high" and dizziness. He experienced a focal seizure. He was on Lithium 300 mg tid and had a low serum sodium but this is not given in the laboratory data all of which are normal. Hemogram is not given. (Vol. 1.21, pg. 6?).

#54 received 4 mg Nabilone and complained of drowsiness, fatigue, a floating feeling, myalgia and joint pain. Failed to return for Cycle II.

Two patients on prochlorperazine also failed to return. The complaints were not clear. #47 had sore throat, chest pain, headache, backache and neck ache.

Drug Dose

65% of patients who received Nabilone on day 1 continued drug through day 5 vs. 67% for prochlorperazine. Only eight patients received more than 4 mg on any given day.

In the statistical analysis on every comparison the difference between adverse effects on Nabilone vs. chlorpromazine was either not significant or showed significantly more adverse effects on Nabilone. Despite this 29 of 36 evaluable patients (81%) favored Nabilone.

Vital Signs and Labs

Blood pressure analysis for both recumbent and erect pressures and systolic and diastolic showed either no significance or a larger decrease or smaller increase on Nabilone. Examination of the records showed that a larger portion of the patients had BP recordings complete than under previous investigator. No abnormalities of laboratory data appeared significant on inspection. Elevated SGOT was observed in patients who began the study with elevated SGOT.

Comment:

The incidence of adverse reactions on Nabilone is again high (80%) and always higher than prochlorperazine. No serious reaction is recorded.

NDA 18-677

Protocol 20

Investigator: 306 Bressler -(Vol. 1.11, pg. 205)

This was a small study, 10 patients (4 males and 6 females) were entered. 3 patients terminated the study and 7 were considered evaluable. All patients received at least one dose of Nabilone.

Dropouts:

- #1 received a single 2 mg dose of Nabilone. She experienced hallucinations, nausea, vomiting, nosebleed and also blurred vision lasting 2 days. She continued to feel "high" and dizzy on day 2.
- #9 received 2 X 2 mg doses. She discontinued both drugs for lack of efficacy but later stated Nabilone was better than prochlorperazine.

Blood pressure changes were so seldom recorded they could not be analyzed. No significant laboratory abnormalities were experienced.

80% of patients on Nabilone reported at least one adverse effect and 6 patients had at least 9 occurrences of ADR's related to the nervous system.

Comment:

This short study shows no findings regarding side effects at variance with the previous two studies.

Summary of Protocol 20:

I. Patients receiving at least one dose Nabilone.

Young	(301)	58
Einborn	(302)	43
Bressler	(306)	10
		<u>111</u>

N.B. One patient on open label only was later included in analysis.

II. Early Termination (ADR):

	<u>Nabilone</u>	<u>Prochlorperazine</u>	<u>Unknown</u>
301	3	None	2
302	3	2	None
306	1	0	0

Early Termination (Lack of Efficacy):

301	3 -(4)	3 (4)
302	0	0
306	1	1

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III. # of Patients reporting at least one drug-related adverse experience:

	<u>Nabilone</u>	<u>Prochlorperazine</u>
301	known 33/58 (56.9%) +unknown 47/58 (81%)	11/53 (20.8%) 27/53 (50.9%)
302	known +unknown 34/43 (79.1%)	15/42 (35.7%)
306	known 3/10 (30.0%) +unknown 7/10	None 3/10 (30%)
	<u>K + UK 88/111 = 79%</u>	<u>45/103 = 43.6%</u>

IV. All studies gave highest priorities to nervous system.

Complications: CNS	<u>Nabilone</u>	<u>24.3%</u>
CNS	66.7%	CNS 24.3%
Psychiatric	34.2%	9.7%

<u>Adverse Experience</u>	<u>NABILONE</u> (Total Patients 111)		<u>PROCHLORPERAZINE</u> (Total Patients 103)	
	<u>No. of</u> <u>Patients</u>	<u>Percent</u>	<u>No. of</u> <u>Patients</u>	<u>Percent</u>
Cardiovascular	7	6.3	2	1.9
Eye and Ear	6	5.4	7	6.8
Gastrointestinal	21	18.9	6	5.8
Genito-Urinary	1	0.9	2	1.9
Metabolic and Endocrine	1	0.9	0	-
Miscellaneous	25	22.5	20	19.4
Musculoskeletal	2	1.8	6	5.8
Nervous System	74	66.7	25	24.3
Psychiatric	38	34.2	10	9.7
Respiratory	5	4.5	2	1.9
Skin and Appendages	0	-	1	1.0

N.B. Hypotension, hypotension orthostatic, and syncope were rare (Nabilone 8/8 and prochlorperazine 2/2) considering that the general trend was to a drop in BP with Nabilone and a rise in BP with prochlorperazine. No instance was reported as severe. Only 75/126 had blood pressure follow-up.

NDA 18-677

Protocol 28

Title: A placebo-controlled study of the antiemetic effectiveness and safety of Nabilone in patients with nausea and vomiting caused by cancer chemotherapy.

Study Plan:

This was a multicenter double-blind, randomized, crossover study comparing Nabilone with placebo given during two consecutive cycles of cancer chemotherapy involving 6 investigators.

Study Design:

<u>Cycle 1</u>	<u>Washout</u>	<u>Cycle 2</u>	
<u>Day</u>	<u>3-6 Weeks</u>	<u>Day</u>	
<u>1,2,3,4,5</u>		<u>1,2,3,4,5</u>	
Group 1 Nabilone		Placebo	Open Label
Group 2 Placebo		Nabilone	Nabilone

Only patients expected to remain on the same regime of cancer chemotherapy during the two consecutive cycles of the crossover study were included. Patients on high dose Cis-platinum (over 100 mg/M²) were excluded (cf. Protocol 20). Patient assignment was stratified to ensure balanced distribution of patients who have not had prior cancer chemotherapy and those who have had prior chemotherapy. Drug dose was 2 mg bid.

Study 001 Jones:

24 patients (8 males and 16 females) ages 20 to 78 were enrolled. 11 were considered evaluable (less than 50%). 22 patients received at least one dose of Nabilone. 11 patients discontinued the crossover study early.

II. Diagnosis:

- 8 = lymphoma
- 4 = breast cancer
- 4 = ovarian cancer
- 8 = other

III. Cisplatin:

6 received cisplatin in one of the cycles
18 did not receive cisplatin.

IV. Dropouts:

4 due to adverse experience - Nabilone - 104, 109, 118, 126

Nabilone related adverse experiences:

- 1. dizzy, drowsy, orthostatic hypotension
- 2. dizziness, nausea and vomiting
- 3. drowsiness, dizziness and ataxia
- 4. drowsiness, dizziness

2 due to adverse experience on placebo -#113, 115

1 due to lack of efficacy on Nabilone - 120

2 due to lack of efficacy on placebo -#116, 121

3 patients (open label) discontinued for intoxicated feeling, orthostatic hypotension, drowsiness and dizziness.

V. ADR's:

18 of 22 patients (82%) on Nabilone had at least one adverse experience vs. 4 of 21 patients (19%) on placebo.

The usual predominance of CNS symptoms was observed. Most were "mild or moderate" in severity. Hypotension was present in 3 patients.

Age, sex and dose were not related to incidence of adverse reactions. 2 patients (one open label) discontinued for orthostatic hypotension.

Investigators global impressions clearly favored placebo over Nabilone (Nabilone 1.64 vs. placebo 0.18 - (Mean Values)

Only one episode of hypotension is described during the study proper and this was considered severe (3) but blood pressure recordings are incomplete in crossover and therefore cannot be meaningfully compared.

Laboratory abnormalities were generally present at baseline and could not be attributed to drug.

Comment: This is a small study in which many factors do not reach significance especially with more than 50% of patients excluded.

Adverse reactions were in the 80% range with Nabilone and much higher than placebo.

Orthostatic hypotension occurred only with Nabilone.

NDJ. 18-677

Protocol 28

Investigator 002 Einhorn:

Study is still in progress. This is a report of the findings to date (1982).

42 patients (23 males and 19 females) between the ages of 16 and 63 were enrolled. 42 were evaluated for safety (at least one dose of drug).

33 patients were considered evaluable and the investigator's global impression of adverse experiences are available for these and indicate that placebo was better than Nabilone in 32 of 33 patients (p .001).

There was a striking difference in the vomit frequency for Cycle I vs. Cycle II.

I. Dropouts:

4 patients discontinued the crossover study early due to adverse experiences vs. none on placebo. 4 discontinued due to lack of efficacy on placebo.

Adverse Experiences:

- #204 - 2 doses of 2 mg Nabilone gave sleepiness, lightheadedness, dysphoria and decreased coordination before chemotherapy started.
- #205 - One 2 mg dose; severe vertigo, nervousness and dry mouth.
- #224 - 2 doses of 2 mg Nabilone; drowsiness, dizziness, dry mouth, headache and dysphoria.
- #237 - 4 days of Nabilone. Patient experienced drowsiness, lightheadedness, orthostatic hypotension.

II. Drug:

9 out of 21 patients received cisplatin.

40 patients took drug on day 1 but only 19 on day 2 and less thereafter. 14 took 5 days of Rx.

111.41 of 42 patients (98%) experienced at least one adverse effect.

4 of 35 patients (11%) who received placebo experienced at least one adverse effect.

CNS symptoms predominated as in other studies.

4 patients experienced orthostatic hypotension - severe.

Sex, age and dose were not related to incidence of adverse experiences.

Blood pressure fell in all measurements to a statistically significant degree. A significant proportion of patients had more than one BP recorded.

2 patients on open label dropped out due to adverse experiences.

Laboratory data were not significantly abnormal.

Comment:

Again a high percent of adverse effects (98%) was noted with Nabilone.

BP decreases were frequent and 4 cases of orthostatic hypotension were observed.

No like threatening adverse effects occurred.

Patients preferred Nabilone.

Investigator 003 Greco: (Vol. 1-12 (1-11) pg.229)

14 patients (14 males, 10 females) between 37 and 67 years of age were enrolled. 4 patients had ovarian cancer, 4 breast and 4 lung and other. The most frequent therapy was one day of cisplatin, adriamycin, cytoxan and hexamethylmedamine.

11 of the 14 patients received at least one dose of drug and were evaluated for safety.

6 continued an open label study and ADR's are included.

9/11 patients (82%) experienced at least one adverse experience.

1. Dropouts:

One patient dropped out for Nabilone ADR following a 2 mg dose: she experienced hallucinations, was sleepy and incoherent.

One patient discontinued placebo for lack of efficacy.

Investigators global analysis of ADR's showed significant excess in Nabilone over placebo.

Hypotension was not reported but almost no patients had follow-up blood pressures.

Comment: A small study but no significant differences from those of the other investigators was noted.

Investigator 004 Durant: (Vol. 1.12 pg.309)

16 patients (7 males and 9 females) between 26 and 80 years were enrolled. 8 patients were considered evaluable. 5 patients had breast cancer, 4 lung and 2 lymphoma. All 16 patients received at least one dose of Nabilone and all reported at least one adverse experience. No adverse experiences were reported on placebo. Nervous system and psychiatric systems showed the predominant symptoms. No hypotension is reported.

I. Dropouts:

4 patients terminated early due to drug related symptoms; one patient due to lack of efficacy on placebo.

- #405 - One dose of Nabilone followed by a dose of Tigan resulted in continued vomiting prior to chemotherapy. Drug was discontinued.
- #412 - 2 mg dose: weakness, dry mouth, dizziness, insomnia and "strange feelings" - "stoned" of 2-3 days duration.
- #415 - 2 mg dose: dizziness, moderate vomiting and somnolence for 1 day prior to therapy.
- #416 - Completed a 1 day cycle 1 on Nabilone but refused crossover due to drowsiness, dry mouth, nausea and "high."

Median daily score for investigator's global impressions of adverse experiences was 1.38 vs. 0.00.

In general, laboratory values when abnormal were abnormal at baseline.

No evaluation of BP is given, there is no report of hypotension. A small proportion of patients had follow-up blood pressures.

Comment: A small study but the 100% incidence of adverse reactions is typical of Nabilone.

Investigator: 005 Lewitt: (Vol. 1-13, p.12)

This study 's still in progress.

58 patients (25 males and 33 females) age 17-79 were enrolled. 36% had lung cancer, 19% ovarian cancer and 10% breast cancer.

23 out of the 53 patients received Cisplatin as part of their chemotherapy. 51 patients received at least one dose of Nabilone.

The majority of patients received between 2 and 4 mg daily and ADR's were not related to drug dose (or age or sex).

II. Dropouts:

20 patients discontinued the study early.

5 discontinued due to drug related adverse experiences.

1 patient discontinued due to lack of efficacy of placebo and 1 for lack of efficacy of Nabilone.

Drug-Related, Nabilone:

#504 - One day Rx on Cycle II. Dizziness, dry mouth, nausea, decreased coordination and anxiety.

#516 One 2 mg dose: dizziness, sleepiness, anxiety and strange unusual feelings.

#517 - One 2 mg dose: severe dizziness and feeling weird - lasted 1 day.

#566 - One 2 mg dose: shortness of breath, irregular pulse, dizziness and tightness of the chest.

#578 - One 2 mg dose of drug: drunk feeling and dizziness.

#563 - Was noted as related to lack of efficacy of Nabilone - patient refused Cycle II; however, in Cycle I he had refused to continue Nabilone because of felt "weird" on arising; dizzy, drowsy and "high."

#570 - Appears similar. He had drug-related fear, "weird" dizzy feeling and sleepiness during Cycle I. Refused Cycle II because he did not want "to be a guinea pig any more."

III. Results:

47 of 51 patients (92%) who received Nabilone had at least one adverse experience; 7 of 46 patients (15%) who received placebo reported at least one adverse experience. The principle adverse reactions were CNS or psychiatric. No hypotension was related in this study. It is of importance that in this study alone only one of the 58 patients enrolled is not included in the analysis -- all the others had sufficient BP recordings to evaluate changes.

This was borne out by inspection of the patient records. There were significant decreases on Nabilone. Recumbent systolic pressure: 41 decreases vs. 5 increases; placebo 16 decreases vs. 17 increases. Diastolic BP 18 decreases vs. 6 increases. Placebo 6 vs. 9 (.022 vs. .500). Standing blood pressure was even more impressive systolic. Nabilone 41 decreases vs. 2 increases (p .001) vs. 16 to 17 (p .500) for placebo and 14 to 6 (p .116) for Nabilone vs. 4 to 9 for placebo (.226) for placebo. Diastolic: 14 decreases to 6 (p .116) for Nabilone vs. 4 to 9 for placebo (.226).

CANCER CHEMOTHERAPY BY EVALUABILITY AND SEQUENCE GROUP

Chemotherapy	Evaluable Treatment			Unevaluable Treatment		
	Group 1	Group 2	Total	Group 1	Group 2	Total
	Cisplatin + Other Combinations	19	26	45	15	8
Other Combinations Without Cisplatin	<u>38</u>	<u>46</u>	<u>84</u>	<u>26</u>	<u>21</u>	<u>47</u>
TOTAL	57	72	129	41	29	70

The total daily dose of Nabilone taken by the patients were analyzed and the results were shown in Table 2. The most frequent dose was 4 mg a day on the first day of chemotherapy. Of 167 patients who received Nabilone on Day 1, 20 patients (12%) continued to take Nabilone through Day 5.

FREQUENCY OF PATIENTS BY TOTAL DAILY DOSE
(Composite of All Six Investigators)

Total Daily Dose	Treatment Day								
	0	1	2	3	4	5	6	7	8
2 mg	183	22	6	2	2	3	-	-	-
4 mg	<u>0</u>	<u>145</u>	<u>25</u>	<u>21</u>	<u>19</u>	<u>17</u>	<u>-</u>	<u>1</u>	<u>1</u>
TOTAL	183	167	31	23	21	20	0	1	1

Adverse experiences were examined in 183 (of 199) patients who received at least one dose of Nabilone, and in 165 patients who received at least one dose of placebo.

168 patients (87.4%) on Nabilone and 18 of 165 patients on placebo (10.9%) reported at least one adverse experience - related to drug or unknown was not distinguished.

The most frequent symptoms on Nabilone were vertigo, dizziness and dry mouth. Ataxia and depersonalization were common. Drowsiness and vertigo were the most frequent adverse effects complained of on placebo.

The comparison of investigator's global impression of adverse effects was equally striking: means were 1.33 for Nabilone vs. 0.06 for placebo.

Among patients who chose to continue on open label study 53/55 reported adverse symptoms.

This bears out the prior experiences where less complete records were available. As in other studies global impressions of adverse effects were strongly in favor of placebo (p .001).

Comment:

This is a very well carried out study; certainly the BP recordings are much more complete than in any of the other studies. Yet the results do not differ significantly from the others. This study of blood pressure could be considered pivotal.

Investigator 006 Gunnell (Vol. 1.13, p.210)

45 patients (20 males and 25 females) in and outpatients between the ages of 29 and 78 were enrolled. 31% had breast cancer, 22% lung cancer and 9% ovarian cancer.

36 patients were evaluable. 10/45 patients received Cisplatin.

41 patients received at least one dose of Nabilone.

I. Dropouts:

4 patients terminated early due to adverse experiences on Nabilone.
3 patients on placebo terminated early due to lack of efficacy.

- #609 - Completed Cycle I (Nabilone) refused Cycle II because of severe dysphonia, dizziness, and decreased coordination.
- #625 - One 2 mg dose of Nabilone; severe lightheadedness, dysphonia and dullness.
- #639 - Day of Cycle I only - (74 mg) severe drowsiness, dysphonia and dizziness.
- #704 - Completed Cycle I, refused Cycle II because of severe drowsiness, dry mouth, moderate lightheadedness, confusion and euphoria.

II. Drug:

Only 1 patient took 5 days of Nabilone. 40 took at least one day of Rx.

Results:

32 of 41 patients (78%) who received Nabilone reported at least one adverse experience as against 2/41 patients who received placebo. The usual predominance of CNS symptoms and psychiatric symptoms was observed; vertigo, drowsiness, dry mouth and euphoria were most common. One episode of hypotension was noted.

They report no statistically significant decrease in BP with Nabilone over placebo, but the records have few follow-up blood pressures. Age, sex and dose had no effect on the incidence of adverse effects. Laboratory abnormalities were not significant. Global estimate of adverse reactions favored placebo over Nabilone (p .001).

Comment:

This is an unfinished study.

Blood pressures were not recorded in a number of instances or no follow-up blood pressure was recorded; one episode of hypotension occurred.

Findings did not differ from the other studies.

Summary: Protocol 28 (Vol. 1-11, p.249)

A total of 199 patients (87 males and 112 females) were studied by 6 clinical investigations in which a double-blind crossover study compared the antiemetic effects of Nabilone to placebo. The patients were in the ages of 17 and 80 years. Ninety-eight patients were studied in the Treatment Group 1 and 101 in Treatment Group 2. Of these 199 patients, 129 (55 males and 74 females) were considered evaluable. Fifty-seven of evaluable patients were in the Treatment Group 1 and 72 were in the Treatment Group 2. More patients under the Treatment Group 1 were found to be unevaluable (41 of 98 patients) compared to the patients in the Treatment Group 2 (29 of 101 patients). The reason was that 16 patients terminated the study early because of adverse experiences while receiving Nabilone.

Fifty-two patients (26%) had breast cancer, 38 (19%) lung cancer, 23 (12%) ovarian cancer, 23 (12%) testicular cancer, and 23 (12%) lymphoma including Hodgkin's disease. The remaining 40 patients (19%) had many other types of cancers with the patient frequency of 4 or less for each cancer.

The most common cancer chemotherapy regimens consisted of Adriamycin and cyclophosphamide in various combinations with one or two other agents, or Cisplatin and Adriamycin in various combinations with one or few other agents. However, a break down of the cancer chemotherapy agents were made into two major groups with respect to Cisplatin and the frequency of both evaluable and unevaluable patients in each group was presented in Table 1. Of 109 evaluable patients, 84 received combinations of chemotherapy regimen with Cisplatin.

**ADVERSE EXPERIENCES OCCURRING WITH A 5% OR GREATER
INCIDENCE DURING THE CROSSOVER STUDIES
AND DURING OPEN-LABEL STUDIES**

(Drug-Related and Unknown Drug Relationship)

<u>Adverse Experience</u>	<u>Total Patients: 183</u>	
	<u>No. of Patients</u>	<u>Percent</u>
Drowsiness	110	60.1
Vertigo	109	59.6
Salivary Secretion Disturbance (Dry Mouth)	66	36.1
Ataxia	22	12.0
Depersonalization Syndrome	22	12.0
Sleep Disturbance	20	10.9
Dysphoria	19	10.4
Euphoria	18	9.8
Headache	17	9.3
Nausea	13	7.1
Disorientation	11	6.0
Concentration Decreased	10	5.5

SUMMARY OF REASONS TERMINATED

<u>Reason</u>	<u>No. of Patients</u>
Nabilone-Related Adverse Experiences	22
Placebo-Related Adverse Experiences	2
Adverse Experiences - Unknown or no Drug Relationship	3
Lack of Efficacy - Placebo	12
Lack of Efficacy - Nabilone	2
Lost to Followup	5
Patient Decision	6
Chemotherapy Changed	7
Progressive Cancer	2
Death (Cancer)	5
Complicating Conditions	1
TOTAL EARLY TERMINATIONS	67

Total Signs and Laboratory Data:

The records of blood pressure recordings are grossly deficient. Analysis of blood pressure was performed on 127 of a total of 199 patients. However, most studies did not have consistent, repeated measurements during both cycles of the study, and often only 2 blood pressures, one a baseline study are recorded.

The exception to this is Study 005 Lewitt (Vol. 1-13, p.12). In this study all but one patient had frequent blood pressure recordings. The results clearly show a significant fall in both systolic and diastolic and erect and recumbent blood pressures on Nabilone. This study involving 58 patients could stand as a pivotal study of blood pressure. The changes confirm the analysis of the whole study which reported significant decreases in blood pressure (.02) with Nabilone.

Orthostatic hypotension was reported in 7 patients (3.8%). These are probably relatively severe reactions.

Adverse experiences were not analyzed for severity. Inspection of patient records show that a number were rated 3 or severe. An analysis of the severity of reactions could be prepared by the sponsor from data available.

Most important and in keeping with the development of tolerance with Nabilone is the fact that the majority of dropouts for adverse reaction occurred in patients who had only a single 2 mg dose.

It may be important to use rising doses and warn of adverse experiences to the patients if this were recommended as a back up drug for cancer chemotherapy nausea and vomiting.

Protocol #7 (Vol. 1.15, pg.1)

Title: Nabilone vs. Prochlorperazine in the Treatment of Nausea and Vomiting in Cancer Patients Undergoing Chemotherapy.

This was a double-blind, randomized crossover trial comparing the antiemetic effectiveness of Nabilone with that of Compazine (prochlorperazine) in patients with severe nausea and vomiting associated with anticancer chemotherapy.

The crossover was similar to the other controlled studies. The cycles is a course of chemotherapy usually administered over a 1-5 day period. The patient received either Nabilone or prochlorperazine in the first cycle and was crossed over to the other drug in the second cycle usually 3-6 weeks apart. The first dose of drug was administered on the evening prior to the first day of chemotherapy. Dose varied from 1 to 6 mg per day.

NDA 18-677

Efficacy and side effects were determined by a diary kept during the treatment period rating a) nausea and vomiting, b) euphoria, dry mouth, drowsiness, tachycardia and postural hypotension, time or distance distortion and inability to perform tasks requiring time coordination.

Subjects were interviewed daily. 43 patients age 17 to 70 years, 18 males and 25 females were enrolled. Fourteen patients were excluded due to protocol violations. 30 patients completed both cycles. 6 patients received cisplatin plus other chemotherapy. 17 received adriamycin plus other chemotherapies. The most frequent treatment was bleomycin, nitrogen mustard, procarbazine and vincristine. Most multiple chemotherapy occurred on days 1 or 2. All 43 patients received Nabilone but only 37 patients received Compazine.

Results:

1. Dropouts: 5 (78) patients terminated early due to Nabilone related side effects and 2 due to prochlorperazine.

#10 -discontinued drug after second 2 mg dose due to orthostatic hypotension with syncope.

#23 -following one 2 mg dose patient complained of decreased appetite, decreased concentration and coordination, dizziness, drowsiness and dry mouth and refused to continue.

#48 -patient is scored as discontinuing due to both Nabilone and prochlorperazine. Cycle I was Nabilone and she experienced severe headache, pruritus and decreased appetite following 10 mg of prochlorperazine in Cycle II and discontinued the study. No description of Nabilone symptoms is given.

#43 -a single 2 mg dose of Nabilone was reported to have produced hallucinations, disorientation and toxic psychosis.

#50 -after one 2 mg dose of Nabilone (Cycle II) experienced decreased appetite, vision disturbance, decreased coordination, dizziness, drowsiness, dry mouth, euphoria, headache, hypotension, excess perspiration, weakness, nausea and vomiting prior to anti-cancer chemotherapy and discontinued drug.

#16 -discontinued after a full 6 day course of 6 mg of Nabilone due to side effects, mild to moderate drowsiness, visual disturbance, confusion, constipation, dizziness, dry mouth, euphoria, decreased urinary output and headache.

#28 -complained of nausea, dizziness, dry mouth and a "high" after the first 2 mg dose of Nabilone and refused to continue.

NDA 18-677

#29 -on a daily 6 mg dose complained of decreased appetite, vision disturbance, decreased coordination, depression, dizziness and dry mouth and refused to continue study.

#45 -reported nausea and vomiting prior to chemotherapy on 10 mg of prochlorperazine.

Drowsiness, dizziness and dry mouth were the most frequent complications. All of the 43 patients who received Nabilone (100%) and 35/37 patients who received prochlorperazine reported at least one adverse experience.

NUMBER OF PATIENTS REPORTING AT LEAST ONE ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE BY BODY SYSTEM

(Drug Related and Unknown Drug Relationship)

Body System	NABILONE (Total Patients 43)		PROCHLORPERAZINE (Total Patients 37)	
	No. of Patients	Percent	No. of Patients	Percent
Cardiovascular	15	34.9	3	8.1
Eye and Ear	24	55.8	8	21.6
Gastrointestinal	38	88.4	24	64.9
Genito-Urinary	6	14.0	4	10.8
Miscellaneous	20	46.5	17	45.9
Nervous System	43	100.0	27	73.0
Psychiatric	26	60.5	7	18.9
Skin and Appendages	3	7.0	1	2.7

Changes in blood pressure were significant only on recumbent systolic blood pressure. 10 patients had a greater decrease while on Nabilone while 2 had a greater decrease on prochlorperazine. Most patients had more than one B.P. recorded.

Comment:

This study of 48 patients is significant for safety data and confirms the high incidence of adverse effects on Nabilone. Syncope is reported from one case of orthostatic hypotension and the incidence of orthostatic hypotension was 18.6% vs. 0 for prochlorperazine.

This confirms data from other studies.

Protocol #9: (Einhorn, Indiana University) Vol. 1.14, pg.1

This was a double-blind, randomized crossover study evaluating the effectiveness and safety of Nabilone compared with prochlorperazine in the treatment of nausea and vomiting in cancer patients receiving chemotherapy.

The study plan included two cycles of chemotherapy 2-4 weeks apart with 1-5 days of chemotherapy at the beginning of each cycle with the first dose of study drug given 30 minutes prior to chemotherapy.

Dose: Nabilone was administered as a 1 mg capsule q 6h. p.r.n. and prochlorperazine as 5 mg capsule q 6h. p.r.n. The protocol was later amended so that the first dose was given on the evening before the first day of chemotherapy.

98 patients (83 males and 15 females) between the ages of 15 and 74. Two additional patients (101 and 102) were admitted directly to open label Nabilone and were evaluated for safety only. 52 of 96 patients (54.2%) continued Nabilone on an open label basis. One patient was entered twice (#12 and 67) and was evaluated for safety both times.

Results:

1. Dropouts:

5 patients discontinued Nabilone because of adverse experiences. None discontinued prochlorperazine as a result of adverse experiences.

#11- Following 4 mg of Nabilone the patient experienced a high, moderate drowsiness, dizziness, depression, and reported feeling more anxious. She chose not to continue the drug. She reported having had a similar reaction on tylenol.

#14- Following 2 X 2 mg doses she complained of dizziness, nausea, bizarre dreams, strong and rapid heart beat and discontinued the drug.

#15- Took 3 days of drug (14 mg) and complained of a high, dizziness, severe drowsiness, dry mouth and difficult speech. She did not continue.

#44- After 2 mg of Nabilone in cycle II reported moderate drowsiness, depression and a high. He did not like how it made him feel and discontinued the drug.

No clear-cut 5th patient who discontinued because of Nabilone is reported.

NDA 18-677

II. 83 of 98 patients were considered evaluable.

76 of the patients had testicular cancer.

86 patients received Cisplatin with other combinations. Multiple drugs were usually given the first 2 days.

58/94 patients who received drug on day 1 (72%) received drug through day 5. The most frequent daily dose of Nabilone was 4 gm.

III. 96 patients received at least one dose of Nabilone.

90/96 patients (93.8%) reported at least one adverse experience.

74/92 patients taking prochlorperazine reported at least one adverse experience.

Adverse experiences were most frequently nervous or psychiatric as in previous studies. Drowsiness, vertigo, and a "high" were the most common reactions on Nabilone. 3 patients experienced orthostatic hypotension and one had syncope.

A significantly greater proportion of decreases of blood pressure were observed on Nabilone - (recumbent diastolic p 0-043), standing systolic (p .001) and standing diastolic (p .004). Most patients had more than one BP recorded in each cycle.

No laboratory abnormalities were considered significant by the investigator.

NUMBER OF PATIENTS REPORTING AT LEAST ONE
ADVERSE EXPERIENCE WHILE RECEIVING NABILONE OR PROCHLORPERAZINE
BY BODY SYSTEM

(Drug Related and Unknown Relationship)

Body System	Nabilone (96 Patients)		Prochlorperazine (92 Patients)	
	No. of Patients	Percent	No. of Patients	Percent
Cardiovascular	5	5.2	2	2.2
Eye and Ear	2	2.1	1	1.1
Gastrointestinal	3	3.1	27	29.3
Miscellaneous	25	26.0	69	75.0
Nervous System	88	91.7	11	12.0
Psychiatric	49	51.0		

Comment: This is a relatively small protocol but all findings confirm those reported in other studies. Initial doses of Mabilone of 1 mg were not associated with dropout; one assumes that 2 mg was adopted as the dosage form because adverse reactions on the lower dose were less significant.

Summary of adverse reactions in prochlorperazine controlled studies (Protocols 7, 9, and 20).

	(#7)		(#9)		(#20)	
	N	P	N	P	N	P
Patients	43	37	96	92	111	103
ADR	43(100%)	35(95%)	90(96%)	74(80.4%)	88(79%)	45(43.6%)

Dropouts due to ADR's Protocols:

Summary #7, 9, and 20: (Total 18)

2 mg - 9
4 mg - 3
4 mg - 5

Summary dropouts due to ADR's Protocol 28;

2 mg - 16
4 mg - 3
4 mg - 9 ?+2

Total dropouts due to ADR's:

2 mg - 3
4 mg - 2
4 mg - 3

Totals:

2 mg - 38
4 mg - 8
4 mg - 15

Thus more than 3/4 of the patients who dropped out for Mabilone side effects had a dose of less than 4 mg; and most patients stopped the drug after a single 2 mg dose.

Analysis of Dropouts:

I. Study 7, 9, 20 and 28.

General:

Because the incidence of adverse effects is virtually 100% and because the patients receiving multiple chemotherapy for cancer were so sick the adverse effects were generally related without an attempt to distinguish those cases already drug-related and those that were not. A standard form -- the Modified Cornell Medical Index (Vol. 1.9, Appendix III) was used throughout as a daily questionnaire to report adverse effects. The investigator was asked, where possible, to give an impression of the relationship of each adverse effect to drug. Most were listed together whether known or unknown.

Laboratory data were given in detail with high and low values indicated.

In Protocol 28 the abnormal data are listed separately in sections C-4 and C-5. If a low WBC was found the patient number and all WBC's were given.

In perusing the laboratory data some are unexplained and remained high throughout a number of determinations but generally, a) they were high at baseline, and b) the high values were not seriously elevated.

In each protocol the investigator was asked to evaluate the laboratory data and no serious reactions are described or attributed to the drug.

Vital signs and blood pressures were recorded but inconsistent. In statistical analysis the decreases of BP on Nabilone were significant. In only one study were BP's faithfully recorded (005-Lewitt). This study in which 58/59 patients had recorded BP's showed a decrease on Nabilone and this could stand as a significant study by itself.

Despite the tendency to low blood pressure only one patient was dropped out for syncope or orthostatic hypotension.

It is of interest that the majority of dropouts had received only a single 2 mg dose of Nabilone. In one study starting at 1 mg doses no comparable severe reactions are recorded. It suggests along with the evidence for rapidly developing tolerance, starting early with a low dose might be a reasonable strategy for using this drug.

II. Summary of patients with at least one adverse reaction:

(7) 43/43 or 100%	Prochlorperazine	35/37
(9) 90/96		74/92 (or) 154/232 (or) 66%
(20) 88/111		45/103
(28) 168/183 vs.	Placebo	18/165

TOTAL - 389 of 433 patients (or) 89%

I. Dose Ranging Studies:

Protocol 1 - Lemberger: (Vol. 1.9, p.242)

3 subjects, inmates of Indiana Reformatory, received Nabilone as a co-precipitate with PVP in single oral doses of 0.1 to 5 mg. Doses were separated by at least 5 days in all three subjects, and the studies were single-blind with a placebo control. Side effects were elicited by a modified Cornell Medical Index. BP recordings were prior to drug and at varying intervals thereafter.

Results: The effects were dose related. At doses less than 3 mg there were no significant findings. At doses above 3 mg all subjects had dry mouth and euphoria. After 5 mg all subjects complained of dizziness on assuming the upright position, postural hypotension and slight tachycardia was documented.

It is interesting that subject _____ described a "high" on placebo on at least two occasions.

Protocol 1 - Amendment 1, 2, and 3: (Vol 1.9, p.258)

Amendment 1 was to allow determination of plasma levels with a single dose of drug. Method developed for this is described in the appendix.

Amendment 2 was to enroll 6 additional subjects to obtain plasma level data.

Amendment 3 was to admit 1-2 additional subjects for plasma level.

Results: 9 additional male volunteers were used. All received a single 2 mg dose of Nabilone. All were administered a modified Cornell Medical Index.

Results:

- 2/9 had no adverse experience
- 6/9 had dizziness or lightheadedness
- 7/9 drowsiness
- 4/9 euphoria
- 4/9 dry mouth
- 2/9 elation
- 2/9 headache
- 1/9 a different taste
- 1/9 had documented postural hypotension

Comment: This suggests that although inconsequential, side effects are experienced at doses less than 3 mg.

Protocol 2: (Vol. 1.9, p.283)

Effects of multiple doses of Compound 10951Y (Nabilone) in human male volunteers.

3 subjects given: (1) 1 mg bid X 7 days X 1 subject
(2) 2 mg bid X 7 days X 3 subjects
(3) 5 mg a single dose on day 7 X 3 subjects

- (1) The first patient showed mild symptoms on day 2 which disappeared.
- (2) On 2 mg bid all developed symptoms on day 2 and later were tolerant.
- (3) On a single added 5 mg dose after 7 days treatment minimal increases in Cornell Medical Index developed.
- (4) One week later challenge with 5 mg produced more marked effect.
- (5) Discontinuing drug was not accompanied by signs of abstinence.
- (6) A single subject received 50 μ C of ^{14} C labelled drug (without PVP) only 76% was recovered in feces and 4% in urine. This analysis was borne out by examination of the data. The blood pressure changes were inconsequential.

Amendment 1: (Vol. 1.9, p.325)

Nabilone 1 mg tid was given for 14 days to 6 normal volunteers. No placebo control was used.

Results: Standing BP was reduced (in 38 subjects) for the first few days and dry mouth and euphoria were common complaints. Tolerance was noted. By day 14 no untoward effects were noted. No withdrawal effects were noted.

Comment: Plasma concentrations and rates of decay following chronic administration (1 mg tid X 14 days) were similar to those following single doses. There is no evidence of drug accumulation. Safety, dry taste, headache were common and subsided with continued administration.

Protocol 7 - Bressler: Part I. (Vol. 1.8, p.424)

Objective: To evaluate the effectiveness and safety of Nabilone in the treatment of nausea and vomiting in patients receiving cancer chemotherapy. Part I dose ranging (Part II compared to prochlorperazine).

13 patients who had experienced severe nausea and vomiting associated with parenteral cancer chemotherapy and who had been resistant to treatment with prochlorperazine were randomized to receive either 1 mg tid or 2 mg tid of Nabilone beginning 30 minutes prior to chemotherapy.

Efficacy: Therapeutic response was rated as none, partial or complete by the investigator.

Safety: Toxicity was rated as mild, moderate or severe.

Results:

Efficacy: <u>1 mg</u> none	- 1	<u>2 mg</u> none	- 0
partial	- 5	partial	- 5
partial-complete	- 1	partial-complete	- 1
complete	- 0	complete	- 0

Toxicity: Dizziness, decreased coordination, drowsiness and dry mouth were most common (approx. 50%). 3 patients had severe reactions at each dose. No labs were abnormal.

It is stated that the investigators noted a feeling of dissociation which tended to persist 2-3 days after the Nabilone was discontinued.

Comment: Dose made no apparent difference in either effect or toxicity. Most all patients experienced some side effects - none serious.

II. Metabolism:

Protocol 3 - Lemberger: (Vol. 1.8, p.1)

Clinical Pharmacology Intravenous Study.

8 male patients received a single IV dose of either 0.25 mg, 0.5 mg or 1 mg to evaluate pharmacokinetics, metabolism and safety. (6 X 0.5 - 1 X 0.25 - 1 X 1.0). This was also a dose-finding study and the 1 mg dose was followed by marked side effects and the 2 mg dose was never given.

Results: 67% in feces and 20% in urine (7 metabolites in urine). After a single IV dose of ¹⁴C-Nabilone 0.5 mg mean plasma half-life was 20.6 hours. Estimated half-life of parent compared was 1.7 hours.

Side Effects: The one subject receiving a 1 mg dose was in acute distress describing a feeling of "emptiness, euphoria, restlessness, numbness, drowsiness and epigastric distress. This subsided promptly but there was a decrease in sensorium lasting 24-36 hours. One patient experienced postural hypotension. Six experienced dizziness, tachycardia, drowsiness and headache fatigue and euphoria. Only one patient had no side effects.

Comment: There is a limitation on IV dosage of this drug and most patients have drug-related side effects.

Protocol 5: Lemberger (Vol. 1.8, p.15)

The disposition and metabolism of compound 109514 (Nabilone) in normal volunteers.

Study Oral: ¹⁴C Nabilone was administered in a single oral dose of 2 mg (50 ¹⁴C Nabilone) in formulation to 2 subjects. Also a third subject received the formulation.

Results: 60% was eliminated in feces. The formulation had low plasma concentrations and more than 9% was excreted in feces unchanged.

Side Effects: Postural hypotension, dizziness, headache and general malaise was reported in the 2 subjects receiving formulation.

Comment: The difference in the formulations is highlighted and the high incidence of side effects with low doses.

III. Bioavailability:

Protocol 30 - Lemberger: (Vol 1.8, p.26)

Bioavailability study of Nabilone containing capsules using Nabilone oral suspension as an in vivo internal reference standard.

Study: Each of 4 males received a single dose of each of 4 formulations of Nabilone; (1) 2 mg, (2) 2 mg, (3) 2 mg, and (4) 2 mg.

Each was given together with 1 mg Nabilone oral suspension.

1 and 2 were bioequivalent, 3 was not, nor to the standard suspension. (See review Hepp - Protocol 30 unacceptable 2/17/82).

Adverse Reactions: All four subjects had side effects, 4/4 dry mouth and dizziness, 3/4 drowsiness and bitter taste, 2/4 weakness, increased appetite and "high".

Comment: Final word on the comparison of studies with different formulations will be needed. The ubiquitous presence of side effects is underlined.

Protocol 31 - Investigator: Lemberger

Objective: To compare the abuse liability of Nabilone to delta-9-tetrahydrocannabinol (THC).

Design: 6 normal, healthy male volunteers who were experienced marijuana smokers capable of recognizing a "high" were assigned 5 regimes in a 5-way crossover study (placebo vs oral Nabilone vs IV Nabilone vs oral THC vs IV THC).

Results: IV THC appeared to be the most preferred of 5 regimes. Nabilone did not appear to produce the same degree of euphoria.

Four psychometric and psychomotor tests were recorded: (1) the wobble-board (balance-seeking movements), (2) attentive motor performance, (3) delayed auditory feedback system, and (4) mirror drawing test to test antianxiety effects.

Adverse experiences are tabulated for each subject but not combined. Drowsiness, decreased salivation and high were common. The effects were not qualitatively different than those to THC.

Comment: The similarity of adverse effects of Nabilone to those of THC are noted.

Protocol 33 - Dr. Mendelson

Comparative assessment of reinforcing properties of Nabilone and marijuana.

Results in abstract only showed marijuana users chose marijuana. No adverse effects reported.

Protocol 35 - Dr. Lemberger

Dose-Proportionality Study.

This was a four-way crossover study in which four subjects (volunteers) were assigned to four study treatments (1.5 mg Nabilone Suspension, 1 mg Nabilone, 2 mg Nabilone, 3 mg Nabilone) in a random order.

Adverse Experiences: All 4 subjects experienced dry mouth, drowsiness, dizziness. One experienced a high, one was sleepy and one had difficulty sleeping.

Comment: These are similar to other accounts of adverse reactions. All subjects (100%) experienced symptoms.

IX. Antianxiety Studies:

Safety data only - studies 6, 8, 10, 12, 14, 121, 221 with Nabilone in several different doses and diazepam or placebo as control.

This protocol was originally to apply to volunteer subjects age 18 through 48 years who were in good health and not on any treatment for anxiety; they were recruited on the basis of having high levels of state and trait anxiety as described on the basis of Hamilton Anxiety Score, Hopkins Symptom Checklist, Self-Rating Symptom Scale and a Raskin-Covi Rating of 8.

This study enrolled 157 subjects, 50 females and 107 males. In September 1978 it was decided to discontinue the study of Nabilone as an antianxiety agent because of hallucinations and altered mental state in patients who participated in antianxiety and antiemetic studies. Therefore the report gives safety data only and the data were combined from the following investigators.

Type	Controls	Investigator	Study No.	No. of Subjects	Nabilone* Dose (mg)	Frequency
Crossover						
Single-Blind	Placebo	Uhlenhugh	8	9	0.5-4.0	Q-WKx9**
Double-Blind	Placebo	Fann	10	12	1.0-2.5	BID
Parallel						
Dose Ranging	None	Fabre	12	5	1.0-4.0	BID
Double-Blind	Placebo	Fabre	12	20	1.0	TID
Double-Blind	Placebo	Fabre	121	8	1.0	TID
Double-Blind	Placebo +Diazepam*	Aden	14	45	1.0	TID
Double-Blind	Placebo +Diazepam*	Hollister	6	49	2.0	1 dose
Double-Blind	Placebo +Diazepam*	Rickles	221	9	1.0	TID

* Diazepam dose was 5 mg per dose with a frequency matching the corresponding Nabilone schedule.

** Doses were given once-a-week for 9 weeks.

Of the patients enrolled 70 received Nabilone. The 5 continuous dose trials (10, 12, 121; 14, 221) were to last 12-28 days.

Summary: There were no life threatening events. The most frequent reported adverse experiences were dry mouth and drowsiness. No laboratory abnormalities were reported.

Six patients were considered dropouts due to adverse drug experiences. None of the diazepam control patients discontinued for drug.

#10 - This patient had previous drug addictions and alcoholism. After receiving Nabilone 1-2.5 mg for 5 days he developed all acute toxic encephalopathy thought to be secondary to unprescribed drug. He recovered.

#14 - This patient was on 1 mg TID X 3 days. He reported dizziness, headache, dry mouth, nausea and blurred vision and discontinued drug.

#6 - This patient received 1 mg TID for 8 days. She had initial orthostatic hypotension which was not considered related to drug. She had severe headache and nausea considered related to drug and discontinued medication.

#7 - This patient received 1 mg TID and discontinued drug after 2 weeks. She experienced nausea, loss of memory, confusion, a "high", speech defect, weakness, lightheadedness and missing her step. This was considered drug related.

#8 - This patient received 1 mg TID. She took drug for 12 days. She reported feeling moderately high with an increase in anxiety.

Safety Data on 70 Nabilone Patients:

Adverse experiences were not reported by decreasing incidence but dry mouth (21%), drowsiness (15.7%) were the most common symptoms. "High" is listed under CNS symptoms and was reported in 2.9% of patients.

It is noteworthy that in this study a separation was made between adverse experiences thought to be drug related (Table 1) and those not thought drug related. This distribution was not made on other studies and for comparison the results should be combined, e.g., dry mouth 21.4% + 8.6%, dizziness 4.3% + 2.9%.

Comment: The adverse effects reported on these studies are similar to those in other studies although most patients received only 1 mg/dose. The dropouts did not occur at the beginning of the study but after many days of drug administration.

Cesamet in Treatment of Glaucoma :

This study too was discontinued.

17 patients were enrolled and received drug.

5% of the patients reported 78.9% of the adverse effects.

This was a single dose (2 mg/mb) study. 5 patients received multiple doses.

5 serious adverse effects are reported. All but one had their adverse reactions after a single dose. In all a significant blood pressure drop occurred, e.g., to 70/40, 60/40, 60/40, 100/40, and one with "orthostatic hypotension". One patient after a single 1 mg dose was nauseous and fainted.

It is noteworthy that these patients were older than the patients in other studies (all but 2 were > 58 years). The symptoms experienced (excluding hypotension which is not recorded other than in the specific patient descriptions) were nausea, lightheadedness, drowsiness, dry mouth, faintness, giggling and vomiting. 12/17 patients reported minimal or no adverse experiences.

Comment: Most striking in this study is the frequency of hypotension following a single dose in older patients.

Study in "Emergency Use":

60 patients received Nabilone on an "emergency basis" for treatment of nausea and vomiting while receiving chemotherapy.

The drug was administered on an open label basis 2 mg BID the initial dose the night before chemotherapy.

The adverse reactions reported were: dizziness (15.3%), drowsiness (14.6%), dry mouth (6.7%). The others were said to be less than 5% incidence.

Overall Summary: These reports add nothing substantial to the safety reports in completed studies except the possible high incidence of hypotension in older patients with glaucoma.

Summary:

Convincing rationale for amelioration of nausea and vomiting in cancer chemotherapy have been adduced. When in extremis, as many of the patients are, considerations or risk/benefit may be altered from expectations in treatment of less disturbing conditions. Hence one might be prepared to accept a quantity or quality of side effects which might otherwise be considered intolerable. The consideration of using cannabinoids for adjunctive therapy is thus justified. The discussion of safety is undertaken in that light.

An overall review of the toxicity or side effects of Nabilone must take into consideration several factors which are general observations of treatment with Nabilone.

The first is that for practical purposes 100% of patients experience side effects with all doses of Mabilone.

This is most apparent in small Phase I and Phase II studies and in normal volunteers. These effects are generally what would be expected in a cannabinoid and must be evaluated in that light and with a view toward the degree of disability from nausea and vomiting. In the larger controlled studies the incidence of various side effects is tabulated and generally does not reach 100% but they are of the same nature as those reported in early studies; they were expected by the investigators and perhaps by the patients and these tabulations, therefore probably do not reflect accurately the incidence or perhaps even severity of side effects. Patient expectation may have a great deal to do with reporting of side effects; the lack of a "blind" when many patients recognize the drug as compared to active or placebo control may also affect these reports.

Of more practical immediate concern is the relationship of timing and dose to the side effects. In a drug in which for practical purposes there is a 100% incidence of side effects it is important to consider carefully those patients who dropped out of the study because of drug-related effects. The fact that the majority of dropouts occurred after a single 2 mg dose or two 2 mg doses (4 mg) is significant. In the 4 carefully controlled studies 38 patients dropped out after a single 2 mg dose, 8 after 4 mg and only 15 patients who dropped out received more than 4 mg suggesting that side effects severe enough to cause dropout generally occur with the first doses. This is not related to chemotherapy because these doses were administered prior to chemotherapy. It is interesting that in studies where a 1 mg dose was used initially less side effects are reported so that the size of the initial dose may well be important. The rapid development of tolerance is likewise well illustrated in Protocol 2 where rising doses were used in volunteers and a single 5 mg dose was well-tolerated after 7 days of treatment but could not be tolerated when reintroduced after washout. It may well be important that a factor to determine whether the risk/benefit of this drug is adequately to permit its use in severe nausea and vomiting is the size of the initial dose and its time relationship to onset of chemotherapy.

Another general concern is the development of hypotension. Despite the uniform experience of BP decreases (systolic and diastolic, erect and recumbent) the incidence of orthostatic hypotension is the lowest (5.3%) of the side effects reported and in other summaries of 5% or greater incidence disappears altogether. Also only one dropout for hypotension occurred - protocol #7, patient #10 but this required treatment. The record from the study by Levitt the only study in which the blood pressure recordings were complete confirmed the general reports. Thus, hypotension is of concern to the physician using this drug but is not by itself a contraindication to use of the drug but an issue for warning.

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Conclusions:

The safety data on Nabilone show a high incidence of side effects, virtually 100%. Patients who dropped out generally did so after one or two 2 mg doses. Studies of blood pressure show a drop in pressure with Nabilone. The overall incidence of orthostatic hypotension is low but overall incidence less than 5% was not reported and individual instances of hypotension were not uncommon. Some studies are incomplete and a follow-up of years 1982-1984 should be requested with an update of the safety data.

Recommendations:

- (1) Tables of incidence of side effects should be reedited to show incidences of less than 1%.
- (2) Safety data should be updated and included in the above incidence tables.
- (3) The high incidence of dropouts after a single dose of drug should be emphasized and a study performed to elucidate whether slowly increasing doses were better tolerated but still antiemetic.

Cesamet Labeling:

Adverse Reactions:

- (1) A statement that for practical purposes 100% of patients can be expected to experience some adverse reaction with the drug. The most common A.R. are related to the nervous system or psychiatric. Drowsiness, vertigo and dry mouth are the most common. Orthostatic hypotension is a general finding and may result in syncope. This effect may be more prominent in the elderly.
- (2) The incidence of adverse effects should include all reactions including those with an incidence of 1% or less.
- (3) No change in listing by body symptom.
- (4) Data from protocol 28 and 20, 7 and 9 should, as suggested be submitted separately but a summary combining these studies for incidence should also be done.

Dosage and Administration:

- (1) There is evidence that tolerance to the adverse reactions to Cesamet is readily developed. It is suggested that where intolerance of the side effects of Cesamet might be expected to interfere with effective use of the drug dosage can be started with 1 mg 1-2 days prior to administration of chemotherapy slowly increasing to the expected 2 mg dose to be given before the oncolytic agent.

Peggy A. Hanson

Peggy A. Hanson, M.D. (HFN-120)

Review and Evaluation of the Clinical Data of
NDA 18-
677

Applicant: Eli Lilly & Co.
Indianapolis, IN

1. General Information

a. Name of drug:

- (1) Generic - nabilone
- (2) Trade - CESAMET
- (3) Chemical - (+)-trans-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one

b. Category: Cannabinoid

c. Proposed indication: The sponsor is proposing that "Cesamet is indicated for the control of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer."

d. Nabilone will be available in 1 mg (blue and white) and 2 mg (blue and green) pulvules for oral administration.

e. [Marinol, delta-9-THC; Levonantradol (investigational agent)]

2. Manufacturing Controls

I discussed the dosage forms of nabilone with Mr. Zinsitz, the reviewing chemist. He commented that the original formulation was poorly bioavailable and that the sponsor decided to manufacture the dosage form by a different process. Briefly, the initial dosage form contained 2 mg nabilone in a capsule. The bioavailability was poor, as judged by 76% recovery in feces. Peak plasma concentration was observed to be 1 ng/ml at 30 minutes post-administration. To overcome the poor water solubility which resulted in the bioavailability problem, nabilone was dissolved

Following

It was hypothesized that following ingestion, the G.I. contents would dissolve thus liberating nabilone for absorption.

The nabilone: as formulated using two manufacturing procedures, A comparative bioavailability study (Protocol 30) of three nabilone formulations was conducted in four subjects: (1) a nabilone capsule formulation (similar to original formulation); (2) a nabilone/ formulation by the

method (used in the nabilone-prochlorperazine trials - Protocol 20); and (3) a nabilone which is the formulation proposed for marketing. According to the sponsor, the study shows that the two nabilone are bioequivalent. This study has been rejected by Dr. Hepp (see Biopharmaceutics review of 5/27/83) as the sample size does not permit adequate power to detect a 20% difference between formulations and the elimination parameters of nabilone and its metabolites are inadequately characterized. Moreover, the dose proportionality study (Protocol 35) does not appear to be satisfactory in fulfilling the bioavailability requirements (Hepp review, 5/27/83). Neither problem is usually considered to be intrinsically serious enough to cause "non-approval" of the drug product. It is my understanding that Biopharmaceutics is willing to negotiate Phase IV bioavailability and dose-proportionality studies.

3. Pharmacology

a. Pharmacodynamics

Nabilone demonstrated antiemetic activity in two preclinical models, carmustine and mechlorethamine-induced vomiting in the cat and cisplatin-induced vomiting in the pigeon. Nabilone did not block apomorphine emesis in the dog. Interestingly, nabilone was 160 times more potent than prochlorperazine against cisplatin-induced vomiting in the pigeon. Thus, either a species difference or a spectrum of action difference is suggested for nabilone versus prochlorperazine.

Nabilone's effect on spontaneous motor activity and general behavior was assessed in the mouse, rat, cat, dog, and rhesus monkey. The general effect across species was depression of motor activity and depression of normal behavior. These data suggest that nabilone will produce sedative effects in human populations.

Identification of the pharmacological class that nabilone belongs to was conducted under the CPDD testing programs at the Medical College of Virginia and the University of Michigan. Although nabilone was active in two analgesic screening tests, it was not antagonized by naloxone. In morphine-dependent monkeys undergoing withdrawal, nabilone partially suppressed abstinence. Specifically, retching and vomiting were suppressed. However, other signs of abstinence were not antagonized (e.g., mydriasis). Thus, nabilone was considered non-opioid like.

In the rhesus monkey, nabilone produced ptosis, dozing, mydriasis, ataxia and reduced responsiveness to cage mates and observers. In this regard, it was five times as potent as delta-9-tetrahydrocannabinol (delta-9-THC). A 30-day administration of nabilone revealed increasing tolerance to the behavioral effects. In fact, over a 500-fold increase in the original dose failed to elicit nabilone-like activity. Cross-tolerance to delta-9-THC but not morphine was demonstrated.

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There is one preclinical test that is purportedly specific for cannabinoid drugs, the dog static ataxia test. Nabilone and two of its carbinol metabolites were evaluated in this test. Both nabilone and its RRS (6aR, 9S, 10aR) metabolite produced ataxia and body sway at 32 mg/kg, i.v. doses. The SSS (6aS, 9S, 10aS) carbinol metabolite was less active in this test.

b. Pharmacokinetics

The major metabolic transformation of nabilone in all species studied (including man) involves the stereospecific reduction of the 9-keto group to its corresponding carbinols. Nabilone is a racemic (50:50) mixture of two optical isomers, designated RR and SS ketones, which exist in a fixed trans geometry at the 6a, 10a ring junctions. Thus, nabilone is converted to two carbinols, designated the RRS and the SSS carbinols, respectively.

Preclinical studies were conducted in rats, dogs and monkeys using ^{14}C -nabilone to determine its absorption, distribution, metabolism and excretion patterns in these species. In the rat, ^{14}C -nabilone was administered by both oral and intravenous routes. The plasma half-life of total radioactivity was found to be 6 hours following i.v. administration and 20 hours following oral administration.

The ratio of carbinol to nabilone was determined in a separate experiment. Plasma concentrations of "carbinol" were found to be 10 times higher than the parent at 1-, 3-, and 6-hour sampling times. Brain concentrations of the "carbinol" were about 1/2 the plasma concentration.

The feces appeared to be the major excretory route, irrespective of route of administration. However, there was a qualitative difference in that following i.v. administration, biliary excretion of nabilone products occurred as unidentified polar metabolites whereas following oral administration, 50% of the fecal radiocarbon was identified as nabilone. These data indicate that nabilone was incompletely absorbed in the rat.

Oral or intravenous administration of nabilone in the dog resulted in the rapid production of the RRS and SSS carbinol metabolites. Following oral administration, peak plasma levels of nabilone and its carbinol metabolite occurred in two hours. By either route of administration, the ratio of plasma carbinols to nabilone was greater than 4. Further analysis revealed the SSS:RRS ratio to be 5:1. The plasma $t_{1/2}$ after i.v. administration was 1 to 2 hours for the parent and 20 hours for the carbinol metabolites.

Total bioavailability (radioactivity) was calculated to be 25% following oral administration. Nabilone bioavailability was determined to be 7%, indicating extensive biotransformation.

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A tissue distribution experiment of orally administered nabilone to a mongrel dog revealed that all radioactivity could be accounted for by nabilone and its carbinol metabolites. (This is not the case in the beagle dog). Analysis of brain tissue from the mongrel dog revealed that the SSS-carbinol was being concentrated in brain tissue as it exceeded the plasma concentration by a four-fold. All the radioactivity in the cerebral cortex and cerebellum was accounted for by the SSS-carbinol.

A tissue distribution study of ^{14}C -nabilone was performed in 3 beagle dogs. Peak plasma levels of nabilone and its SSS-carbinol metabolite accounted for by the RRS metabolites (which could not be determined due to interference by plasma cholesterol) and other unidentified metabolites. The ratio of the peak SSS-carbinol to nabilone was 5:1. Plasma half-lives were determined to be 4.7 hours for nabilone, 12 hours for the SSS-carbinol and 26 hours for "total radioactivity." Animals were sacrificed 24 hours post-nabilone administration and tissues were assayed for nabilone and its RRS and SSS carbinols. The SSS-carbinol levels in the cerebral cortex and cerebellum were 5 times greater than the plasma concentration. The levels of nabilone and its RRS metabolite were below the limits of detection.

In the monkey, single oral doses of ^{14}C -nabilone equivalent to 0.1, 1 and 10 mg/kg were administered. Peak plasma levels occurred at 2 hours at the two lower doses and at 4 hours at the high dose. At the 1 mg/kg dose, nabilone and its SSS-carbinol metabolite accounted for 10 to 15% of the plasma radioactivity. Plasma half lives were calculated to be 1.5 hours for nabilone, greater than 30 hours for the SSS-carbinol and 10 hours for "total radioactivity." At the 10 mg/kg dose, detectable (> 1 ng/ml) plasma concentrations of the SSS-carbinol were not observed. No explanation was offered for this apparently anomalous result.

In a second study, 0.4 mg/kg ^{14}C -nabilone was administered orally to monkeys. At 2 hours, peak plasma radioactivity occurred with nabilone and its SSS-carbinol metabolite accounting for 28% of the peak plasma radioactivity. The plasma half lives were calculated to be 1.5 hours for nabilone, 3.2 hours for the carbinol metabolite and 11 hours for total "radioactivity." Concentrations of radioactivity in the brain measured 24 hours after dosing were in the 1 to 10 ng/g range; the corresponding plasma level was 10 ng/ml of drug equivalents. Neither nabilone nor the SSS-carbinol could be detected in plasma and brain samples taken at 24 hours. Apparently both the parent and its SSS-carbinols are subject to further metabolism.

^{14}C -nabilone (as _____ was administered to two volunteers. The 2 mg dose produced a C_{max} of 10 ng/ml at 2 hours. The half-life of nabilone was calculated to be 2 hours whereas the $t_{1/2}$ of the total radioactivity was 35 hours. Sixty and 24% of the radioactivity were eliminated in the feces and urine, respectively.

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A 0.5 mg dose of ^{14}C -nabilone was administered intravenously to 5 subjects. The recovery of radioactivity from feces and urine was 67 and 22 percent, respectively.

A study was conducted utilizing non-isotopic nabilone (1 mg t.i.d. for 14 days) in 5 subjects. Plasma was analyzed for nabilone and carbinol metabolites by the GC/MS method of Sullivan which has detection limits of 0.4 and 0.8 ng/ml for nabilone and the "carbinol" metabolites, respectively. The "carbinol" levels ranged from 1.3 to 2.1 ng/ml.

A pilot bioavailability study (Protocol 30) was conducted in 4 subjects. This was a 4-period, 4-treatment crossover study. The two formulations used in the clinical trials (nabilone/prochlorperazine and nabilone/placebo) were compared to a nabilone formulations and a reference suspension. Mean nabilone C_{max} 's were 2.8, 3.8, 1.6 and 5.4 for the four treatments, respectively. T_{max} occurred at 1.3, 1.6, 1.4 and 0.7 hours, respectively.

A pilot dose-proportionality study (Protocol 35) was also conducted in 4 volunteers. nabilone was added to a nabilone suspension and 1, 2, and 3 mg capsules of nabilone. Mean nabilone C_{max} values were 4.0, 1.5, 3.7, and 3.5 ng/ml while mean nabilone T_{max} values were 0.6, 2.3, 1.8, and 4.1 hours, respectively. Based on mean AUC nabilone/AUC D-6 nabilone ratio analysis, dose-proportionality was not demonstrated.

c. Toxicology

Subacute and chronic toxicity studies of nabilone were performed by the oral and i.v. routes in the rat and dog and by the oral route in the dog and monkey, respectively. In the rat, nabilone produced catatonia and hyperirritability to touch following oral administration. These signs rapidly resolved, suggesting tolerance to certain CNS effects of nabilone.

Oral administration of nabilone to beagle dogs in a 92-day study produced ataxia. Tolerance developed to this effect by the end of the second dosing week.

A second oral toxicity study of nabilone (doses of 0.5, 1.0, and 2.0 mg/kg) in dogs, planned for a one-year dosing exposure, was terminated at 7 months due to cumulative toxicity. Two low-dose, 6 mid-dose, and 7 high-dose dogs died or were sacrificed in a moribund condition. Convulsions often preceded death. It was noted that animals usually appeared healthy until near death. (These data caused the interruption of clinical trials in 1979. The agency's position on resumption of clinical trials was that (1) a one-year monkey study should be performed; and (2) carbinol metabolite studies should be performed in species such as the rat and the dog - Kartzinel to Lilly letter - 4/2/80

Subsequently, a five-day i.v. toxicity study comparing nabilone and its SSS-carbinol metabolite was performed in beagle dogs. Signs

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of CNS depression were noted with both drugs. Plasma samples taken from dogs in both groups revealed that SSS carbinol levels were about twice as high in the SSS carbinol-treated group.

A one-year toxicity study of nabilone was performed by nasogastric administration in rhesus monkeys. Sedation and hypoactivity were identified at doses of 0.5 and 2.0 mg/kg. Tolerance developed to the CNS effects. No deaths were observed.

In summary, the major toxicologic finding in the subacute and chronic toxicity studies was the cumulative toxicity of nabilone in the Beagle dog. It was the sponsor's hypothesis that the SSS carbinol (which is formed in the greatest quantities in the dog relative to the rat, monkey and man and is sequestered in the dog's central nervous system) was the toxic moiety. The evidence for this is inferential insofar as the toxicity is observed in the species with the highest conversion to SSS carbinol and not observed in 3 other species in which SSS carbinol levels are far lower. There was an agreement reached by Dr. Contrera with Lilly toxicologists on 5/7/80 that the carbinol metabolite needed further evaluation but could be done "after the NDA process." This should be a formal request if and when an approvable letter is issued.

A secondary issue observed in the animal studies is the development of tolerance to the CNS depressant effects of nabilone. This was confirmed in a pilot study in humans - (See "IND protocol #2" in Vocci drug abuse consulting review of 11/23/82). Whether tolerance develops to the antiemetic effect of nabilone or other side effects is an important issue although the episodic nature of cancer chemotherapy makes it unlikely that a diminished drug effect would occur across treatment episodes. It is possible, however, that tolerance could develop within treatment episodes, especially those lasting more than 5 days.

In reproduction and teratology testing, nabilone decreased food consumption and maternal weight gain. This was linked to a decrease in litter size and an increase in the number of still births. Pup survival rates in nabilone-treated groups were reduced. This may be a result of both maternal and pup characteristics. The dams produced less milk, apparently due to a nabilone influence on prolactin release. The pups were hypothermic which may have been due to an intrauterine effect of nabilone in concert with compromised nutrition.

Nabilone was not teratogenic in standard assay procedures in the rat and rabbit at doses greater than 200 times the proposed human dose.

Nabilone did not produce effects consistent with genetic mutation in the Ames test, sister chromatid exchange test, DNA repair test in rat hepatocytes, dominant lethal test in rats, and micronucleus test in polychromatic erythrocytes in rat bone marrow.

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Carcinogenicity testing with nabilone has not been initiated. This is consistent with the agency policy of a waiver of carcinogenicity testing of anticancer drugs.

4. Clinical background

a. Literature reports

The sponsor has supplied published reports on the chemistry, pharmacology and clinical effects of nabilone. There are four published reports that summarized the results of individual investigators in either the nabilone-prochlorperazine multi-centered trial (Protocol 20) or an open study of nabilone in chemotherapy patients. The reports will be described here and reviewed in greater depth in Section 5 of this review.

- (1) Herman, T.S., Einhorn, L.H., Jones, S.E., Nagy, C., Chester, A.B., Dean, J.C., Furnas, B., Williams, S.D., Leigh, S.A., Dorr, R.T., and Moon, T.E.. Superiority by Nabilone Over Prochlorperazine as an Antiemetic in Patients Receiving Cancer Chemotherapy. N. Eng. J. Med. 300: 1295-1297, 1979.

The authors reported the results of a randomized, double-blind crossover comparison of the antiemetic effect of nabilone versus prochlorperazine in patients receiving cyclic, combination chemotherapy for solid tumors. The studies were performed at the University of Arizona and the Indiana University School of Medicine.

One hundred and fifty-two patients (152) patients were admitted to the study. Fifty-two (52) patients were treated as outpatients at the University of Arizona Cancer Center and 100 were treated as inpatients at Indiana University. The major chemotherapeutic and antiemetic regimens were as follows: (1) 70 patients with testicular carcinoma who received cisplatin (daily for 5 days), vinblastine and bleomycin also received nabilone for 5-1/2 days; (2) 12 patients treated for non-Hodgkin's disease who received cyclophosphamide, doxorubicin, vincristine and prednisone also received nabilone for 1-1/2 days; and (3) 11 patients with Hodgkin's disease who received nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) also received nabilone for 1-1/2 days.

Nabilone was supplied in 1 mg capsules. At the University of Arizona, patients received either 2 mg of nabilone or 10 mg of prochlorperazine every 8 hours beginning two doses prior to chemotherapy. At Indiana University, patients were treated with identical doses every six hours beginning 30 minutes before chemotherapy.

One hundred and thirteen (113) patients completed the crossover. Dropouts were encountered for a variety of reasons: disease progression, unacceptable side effects, insufficient data collected and anticipatory vomiting prior to chemotherapy. Of the five nabilone-treated patients who dropped out due to unacceptable side effects, two had noteworthy adverse experiences: one had orthostatic hypotension which required medical treatment and the other had visual hallucinations and "depersonalization."

Efficacy was evaluated by daily patient ratings of severity of nausea and incidence of vomiting. At the end of each cycle, patients were asked to compare nausea and vomiting with their pretreatment (previous chemotherapy) levels. Scoring was done on a graded scale; i.e., less than 50% response equaled no response, 50% less nausea and vomiting was scored as a partial response, and a complete response was defined as a total absence of nausea and vomiting during a treatment period. At the end of the trial, patients were asked whether they preferred one antiemetic over the other.

Nabilone was superior to prochlorperazine in every efficacy category. Nine (9) patients (8 percent) had a complete response to nabilone. No patient receiving prochlorperazine had a complete response. Eighty-one (81) patients (72%) of the nabilone group had a partial response compared to 36% of the prochlorperazine group ($p < 0.001$, McNemar's test). Additionally, patients recorded less vomiting throughout the treatment cycle when they received nabilone ($p < 0.001$). Further, statistically significant reductions in nausea severity were recorded ($p < 0.05$ to 0.001) for nabilone versus prochlorperazine across treatment days. Finally, 75% of the patients preferred nabilone whereas 18% chose prochlorperazine as the antiemetic of choice ($p < 0.001$).

Common side effects included somnolence, dizziness and dry mouth. Nabilone specific side effects included euphoria (16%), hallucinations (3%), orthostatic hypotension (1%). Even with commonly occurring side effects, those occurring with nabilone were more severe and occurred with a higher incidence.

- (2) Steele, N., Gralla, R.J., Braun, W.W., Jr. and Young, C.W. Double-blind Comparison of the Antiemetic Effects of Nabilone and Prochlorperazine on Chemotherapy-Induced Emesis. Cancer Treat. Rep. 64: 219-224, 1980.

This report summarizes the experience of 31 patients at Memorial Sloan Kettering who participated in a randomized double-blind crossover comparison of nabilone (2 mg) versus prochlorperazine (10 mg) during two successive, identical courses of chemotherapy. Of

note in this report is the analysis of efficacy of the antiemetic as a function of the emetic strength of the chemotherapeutic stimulus. The emetic stimuli administered were (in order of high to low) high dose cisplatin, low dose cisplatin, and mechlorethamine, streptozotocin, actinomycin D or DTIC.

Efficacy parameters assessed the severity of nausea, the frequency and duration of vomiting, and patient preference for either antiemetic.

Safety analysis included a CBC, urinalysis, SMA-12, and electrocardiogram in hospitalized patients during treatment with both antiemetics. Supine and standing blood pressure were monitored every 4 hours during waking hours. Outpatients had a CBC, platelet count, and SMA-12 performed before receiving each drug. The report states that baseline urinalysis and ECG were available. Side effect incidence was tabulated for both patient groups during both antiemetic treatments.

Perception of the duration of nausea varied with the emetic stimulus; i.e., high dose cisplatin low dose cisplatin other regimens. The severity of nausea was more linked to whether the patients were inpatients or outpatients, nausea being more severe in outpatients on comparable treatment regimens.

The duration and severity of vomiting were greater in outpatients who received "other chemotherapy." Neither antiemetic was particularly effective in high dose cisplatin (HD) courses. Emesis was well-controlled in only 2 of 15 courses of chemotherapy on nabilone and 2/15 courses on prochlorperazine. Median duration (but not frequency) of low dose (LD) cisplatin-induced vomiting was reduced more by nabilone than prochlorperazine. Patients receiving "non-cisplatin" courses had reduced frequency and severity of vomiting episodes on nabilone.

Patient preference was analyzed as a function of antiemetic treatment and the order of drug administration. Patients in the LD cisplatin group had a 60% preference for nabilone (20% had no drug preference). Patients in the "other chemotherapy" group expressed a 75% preference for nabilone. An overall preference was recorded for nabilone but this result did not attain statistical significance ($p > 0.05$, binomial test). Order of administration did not affect preference.

One interesting point observed was that 13 of 16 patients correctly guessed they were receiving nabilone ($p < 0.05$, binomial test). This raises the issues of side effect differences unmasking the study blind as well as influencing patient preference and response.

Side effect incidence was lower for prochlorperazine and thus may have been more tolerable. Drowsiness was the only significant side effect that occurred (35% incidence). Nabilone, on the other hand, produced a high degree of somnolence (47%), dizziness (36%) and dry mouth (25%). Side effects were less annoying to the hospitalized patients.

Four patients withdrew from the study due to intolerable nabilone-related side effects. These reactions were characterized as severe dizziness, decreased ability to concentrate, lack of coordination, and dysphoria. One of the dysphoric patients experienced hallucinations, time-space distortion and dyspnea.

Eight patients received further nabilone on an open label basis for one to four more chemotherapy regimens. There was no evidence of a diminished therapeutic effect or reduced side effect incidence.

The authors commented on the low incidence of postural hypotension noted in comparison to other studies. The explanation offered was that this was due to a lack of blood pressure monitoring in the outpatient group.

- (3) Einhorn, L.H., Nagy, C., Furnas, B., and Williams, S.D. Nabilone: An Effective Antiemetic in Patients Receiving Cancer Chemotherapy. *J. Clin. Pharmacol.* 21: 645-655, 1981.

The efficacy portion of this trial has previously been discussed under Herman *et al*, *N. Engl. J. Med.* 300: 1295-1297, 1979. However, one difference in drug administration was cited by the authors. Initially the study drug was administered 30 minutes prior to initiation of chemotherapy; however, the last 44 patients inducted into the protocol received the drug starting 12 hours prior to chemotherapy. There was no explanation given for the change of timing of antiemetic drug administration.

Several observations described are worth noting. The first is that drug preference and antiemesis do not necessarily covary; i.e., 6 patients who chose nabilone experienced less emesis with prochlorperazine and 9 patients who preferred prochlorperazine actually had less emesis on nabilone therapy. The second observation is that the nabilone "high" (not defined by the investigators to the subjects) was dose-related. Twenty of fifty-two patients (38%) receiving 2 to 4 mg/day experienced a "high" while 20 of 28 (71%) of the patients who took 6 to 8 mg/day reported this effect. The third effect of note is that both study drugs produced hypotension in 70 of 80 patients. Nabilone and prochlorperazine were about equivalent in producing blood pressure decreases in the 20 to 29 mmHg range but

nabilone appeared to cause more hypotensive drops of 30 mmHg or greater [36/70 (51%)] than prochlorperazine [20/70 (29%)]. No treatment was needed for the hypotension and chemotherapy proceeded without interruption.

Three patients had syncopal episode; two were attributed to nabilone while the other was prochlorperazine associated.

- (4) Berman, T.S., Jones, S.E., Dean, J., Leigh, S., Dorr, R., Moon, T.E. and Selman, S.E. Nabilone: A potent cannabinol with minimal euphoria. *Biomedicine* 27: 331-334, 1977.

The authors reported the effects of an open design trial of nabilone in 13 patients undergoing cyclic chemotherapy who were refractory to prochlorperazine. Six (6) of the patients received 1 mg every 8 hours and the remaining 7 patients received 2 mg every 8 hours. Nabilone (2 doses) was administered prior to chemotherapy initiation and continued for 5 days. Patients were analyzed as a function of dose per body surface area. The low dose (LD) group received 1.6 to 2.0 mg/m²/day and the high dose (HD) group received 2.6 to 3.6 mg/m²/day.

There was evidence of a dose-effect relationship in that HD patients reported less nausea and vomiting than the LD group. Three patients (2H, 1LD) requested nabilone discontinuation after the first day of chemotherapy due to somnolence in two patients and decreased ability to concentrate in one patient. Orthostatic changes in blood pressure were greatest on day two or three. The most marked change in blood pressure recorded was a drop of 38/22 mmHg in one patient. Postural dizziness occurred in 8/13 patients.

The authors commented that the dosing schedule did not produce marijuana-like "highs" and thus some separation of antiemetic and euphoric effects was noted. However, this may be due to a failure to recognize subtle effects which constitute the "high" on the parts of both investigators and patients. Somnolence, dizziness, decreased concentration, decreased coordination, distortions of time-space perception, feelings of dissociation and affective changes (euphoria, dysphoria, anxiety, panic, transient psychosis) are all symptoms of marijuana intoxication. Older patients who lack prior cannabis experience might not associate some, if not most, of the symptoms with a "high" or euphoriant effect. These same symptoms were reported by patients in varying degrees, thus suggesting coexistence of antiemetic and CNS intoxication associated with nabilone. It may be that only the affective component was being recognized as a "high" or euphoriant effect.

N-18677-3

b. Global comments:

Nausea and vomiting associated with cancer chemotherapy are not clinically trivial events. Repeated vomiting can produce chloride depletion, metabolic alkalosis, dehydration, and hypokalemia. Some of these effects (chloride depletion, metabolic alkalosis, and to some extent dehydration) are a direct consequence of vomiting or inability to maintain an oral fluid intake, whereas the maintenance of the alkalosis and the production of hypokalemia are a result of renal compensatory mechanisms. Other rarer consequences include gastric mucosa rupture and skeletal fractures. (See Penta, J., Poster, D. and Bruno, S. The Pharmacological Treatment of Nausea and Vomiting Caused by Cancer Chemotherapy: A Review. In Antiemetics and Cancer Chemotherapy, ed. J. Laszlo, Williams and Wilkins Press, Balto, Md., 1983).

These facts may have, in part, led to increased sensitivity on the part of oncologists to alleviate drug-induced side effects of chemotherapy. Also, it has been said that this resulted from the current advances in chemotherapy which now can prolong life or even affect cures. This change is reflected in the scientific literature on antiemetic trials. Penta et al (ibid) reviewed antiemetic trials associated with chemotherapy reported in the medical literature from 1960 to 1981. Of the 57 drug trials reviewed, 41 took place in the years 1979 through 1981. Of the studies reviewed, 25/27 used prochlorperazine. It was effective in 13/25 (52%) of the trials. This strongly suggests, among other things, that prochlorperazine is only moderately effective as an antiemetic, not surprising when one considers the heterogeneity of the emetogenic stimuli associated with the various cancer chemotherapy agents.

The relatively recent development of interest in antiemetic drug trials has led many investigators to use various rating scales for nausea and vomiting. In short, there are no uniform criteria for measuring nausea and vomiting. The vomiting scales usually quantify the number of emetic episodes, retching, and, sometimes, the volume of emesis. Such scales have obvious face validity. Other vomiting scales ask patients to determine if a 50% (or greater) reduction in vomiting occurred in comparison to the previous chemotherapy. Responses in such trials may quantify antiemesis as complete, greater than a 50% reduction, or less than a 50% reduction.

The rating scales for nausea are somewhat more problematic. Many investigators have chosen to arbitrarily make up their own nausea rating scales. Some assess nausea alone on a graded basis while others assess the patient's nausea and vomiting simultaneously. To my knowledge, none of these scales have been externally validated. [It may be possible to use a physiological marker of nausea in future drug trials. Rowe et al reported that administration of sub-emetic doses of apomorphine to 10 subjects caused a 60-fold increase in plasma vasopressin (Kidney Int. 16: 729, 1979). Thus, an effective antinauseant may reduce or completely block the elevation of plasma vasopressin.]

While the non-uniform unvalidated rating scales are undesirable and may, in themselves, lead to non-uniform results across trials, they represent an area of clinical pharmacology too new to reach a consensus as to which rating scales (if any) have greater validity.

5. Clinical Studies - Well-Controlled Studies

There are four studies which can be considered well-controlled that could demonstrate efficacy. Protocols 7, 9, and 20 compare the antiemetic effects of nabilone versus prochlorperazine in patients undergoing cancer chemotherapy. In order for nabilone to demonstrate efficacy in these trials, superiority over prochlorperazine needed to be demonstrated. Protocol #28 is a comparison of nabilone versus placebo in patients undergoing cancer chemotherapy. The active control studies will be reviewed first.

a. Protocol #20:

(1) Background:

This was a multicentered trial conducted at three sites. The investigators were Charles Young, New York, (#301), Lawrence Einhorn, Indianapolis (#302), and Rubin Bressler, Tucson, (#306). The Bressler study was interrupted in January, 1979 after 16 patients were enrolled. Seven patients in this study were considered evaluable. However, the statistical analysis demonstrated a significant investigator by residual interaction on vomiting parameters. When the emesis data from investigator #306 were excluded from analysis, the composite analysis of investigators 301 and 302 did not yield a significant investigator by residual interaction.

The sponsor analyzed the efficacy variables from each center in addition to analyzing the composite results. I will review the results of each center and then the composite result.

(2) Study design:

This was a double-blind, randomized, crossover study comparing the safety and effectiveness of nabilone versus prochlorperazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents in two cycles of chemotherapy. Patients were randomly assigned to receive either nabilone or prochlorperazine during the first cycle of chemotherapy and the other drug during the second cycle. The study drug was administered throughout the chemotherapy cycle, which usually lasted 1 to 5 days. Chemotherapy cycles were usually given 3 to 6 weeks apart.

Dosing began on the evening before chemotherapy and continued with administration of study drug 1 hour before and 12 hours thereafter until 24 hours after the cessation of chemotherapy. The dose of nabilone was one (2 mg) capsule, b.i.d. The dose of prochlorperazine was one 10 mg capsule which was identical in appearance to the nabilone capsule.

Inclusion criteria included the following: (1) male or female cancer patients older than age 12 who had received cyclic chemotherapy known to have caused nausea and vomiting during at least two previous consecutive chemotherapy cycles; (2) chemotherapy regimens would remain the same for two consecutive cycles; and (3) written informed consent would be obtained from patients or parental guardian.

Patients were to be excluded from study participation if they had cardiovascular disease, psychotic episodes of a recurring nature or were regular users of marijuana. Females were to be excluded if they were pregnant or not using an appropriate method of contraception.

Efficacy and safety evaluations were recorded on a 24-hour basis. At the completion of the crossover, the patient chose a preferred study drug and the investigator recorded his global impressions of the efficacy and safety of each antiemetic treatment. Patients had the option of continuing with nabilone on an open label basis.

There were three patient-related efficacy variables and two investigator-rated variables during each cycle. Patients recorded the number of vomits per day, the severity of nausea (none, mild, moderate, severe), and food intake (none, less than usual, average for me, more than usual). Investigators rated efficacy (very good, good, fair, poor, and very poor) and the severity of adverse effects [none, did not interfere with patient's functioning, significantly interfered with patient's functioning, (and) outweighed the therapeutic effect.]

Safety parameters included a medical history and physical examination, SMA 12/60, hematology and urinalysis for each patient prior to each cycle of drug administration, including any open label studies. Laboratory tests were to be repeated prior to the next cycle of chemotherapy after the patient had completed the "study drug" portion (2 cycles) of chemotherapy.

Patients recorded adverse reactions on a daily questionnaire which noted the presence of euphoria (a high) and asked to note any other treatment emergent adverse experience.

Patients were randomized according to a pre-determined schedule. The investigator had each patient's drug code in a sealed envelope and referred to it only if he deemed it medically necessary.

In addition to the aforementioned, patient's primary cancer diagnosis, age, sex, intercurrent illnesses, and concomitant medications were recorded.

The following decision rules were used to consider a patient "evaluable": (1) the patient was required to have one or more evaluable days on each cycle; (2) "evaluable" days were the number of days of chemotherapy in which the study drug was administered and "no protocol violations" occurred. The lesser of the two numbers, that is, the number of evaluable days for cycle 1 or the number of evaluable days for cycle 2, was used in the crossover analysis.

Patient rated efficacy variables (vomiting, nausea, food intake) were considered independently when evaluability was assessed. Thus, missing data for one parameter did not exclude the patient's other data from the analysis.

The following situations were deemed "protocol violations":

- (a) a second antiemetic was given other than the study drug assigned by the randomization schedule;
- (b) the study drug was not administered concomitantly with chemotherapy;
- (c) the specific dose of antiemetic, as called by the study protocol was not given prior to chemotherapy; and
- (d) A different cancer chemotherapy regimen was used during the two cycles of chemotherapy on the crossover. Any one of these violations was sufficient to exclude a patient from the efficacy analysis.

(3) Statistical analysis:

Individual investigator results were analyzed for comparability of the sequence groups in both evaluable and unevaluable patients with respect to chemotherapy, prior chemotherapy, sex, and age. When the composite analysis was performed, comparability of sequence groups in both evaluable and unevaluable patients was determined with regard to cancer diagnosis, chemotherapy, prior chemotherapy, sex, age and interaction effects (e.g., investigator by evaluability interaction).

Efficacy and safety data were first described using measures of central tendency and dispersion. If a patient's daily score on a particular variable was missing or unevaluable (continuous vomiting) on one cycle, the alternative cycle's score was eliminated to achieve balance. However, the sponsor used all scores in the non-parametric and contingency analyses.

Data were analyzed using a non-parametric technique appropriate for crossover analysis (Koch, G.G., Biometrics, June, 1972, p. 577-584). Hypotheses concerning direct effects (treatment), crossover effects (residuals) and period effects (cycle) were analyzed using a Wilcoxon two-sample test. The significance level for testing of residuals was $\alpha = 0.10$. If no residual effect occurred, treatment differences were evaluated combining both cycles.

Data were also analyzed for each cycle using the Wilcoxon two-sample test. If a significant residual effect occurred, cycle 1 data were evaluated for treatment effects.

A categorical analysis for each of the efficacy and safety variables examined treatment and cycle effects. Patient preferences were also analyzed by categorical analysis. Differences in response were grouped into three categories (nabilone better, prochlorperazine better, same). Frequencies were analyzed using an exact method for comparing matched proportions in a crossover design (Gart, J.J., Biometrika 56(1): 75-80, 1979). Frequency analysis by cancer chemotherapy dose and/or regimen was also performed. Fisher's Exact Test was used in these tests.

The sponsor also analyzed all cycle 1 patients (both evaluable and unevaluable) using the Wilcoxon two-sample test.

Blood pressure (systolic and diastolic) responses were analyzed by drug for increases versus decreases by a sign test. The test drugs were compared using a sign-test on the pairwise differences from baseline.

All data were analyzed for significance using two-tailed tests. Reviewing statistician's comments (E. Nevius review):

Dr. Nevius commented that the analysis of variance on ranked data had been discussed in the statistical literature, but had not previously been applied to this situation. He did not imply that it was invalid or inappropriate in his review. I communicated with him further on the subject and was told that he felt the analysis of variance was appropriate. Further, Dr. Nevius concluded that the frequency analysis supported the analysis of variance results.

(4) Individual Investigators:

Investigator 301 (Charles Young)

Patients in this study were male and female, in- and outpatients, between the ages of 19 and 68 years old. Sixty-seven patients, 43 male and 24 female, enrolled in the study. The diagnostic frequency is given in Table 1.

Table 1: Frequency of Cancer Type in Study Population

<u>Type</u>	<u>Number</u>	<u>(%)</u>
lung	30	(44.8)
melanoma	7	(9)
bladder	5	(7)
colon	5	(7)
testicle	5	(7)
other	5	(21)

The lung cancer patients received cisplatin and vindesine. The doses of cisplatin were categorized as being above 100 mg/m² or 100 mg/m² or below. Patients were also subgrouped as to whether or not they received cisplatin. Melanoma patients were treated with cyclophosphamide and dacarbazine. Other chemotherapeutic agents administered were adriamycin, chlorambucil, dactinomycin, nitrogen mustard, procarbazine, streptozotocin, vincristine and vinblastine. Within the exception of two patients (#7 and 19), multiple chemotherapeutic agents were administered only on day 1 of the treatment cycle.

Thirty-two (32) of 67 patients enrolled were considered evaluable. Thirteen (13) patients were enrolled but discontinued when the clinical trials were suspended in 1979. The reasons for termination of the study subjects are given in Table 2.

Table 2:
Reasons for Early Terminations
(Sponsor's Table 10, Vol. 1.10, pg 110)

<u>Reason</u>	<u>No. of Patients</u>	<u>Patient Nos.</u>
Drug-related (nabilone)	3	9,28,36
Lack of efficacy (nabilone)	3	11,30,35
Lack of efficacy (prochlorperazine)	3	5,41,43
Lack of efficacy (nabilone and prochlorperazine)	1	39
Adverse experiences (unknown cause)	2	14,52
Protocol violation	2	27,54
Death due to cancer	1	6
Study suspended	<u>13</u>	34,37,57-61, 64-66,68,69, 71,72
Total	28	

Additionally, 7 patients were considered unevaluable due to protocol deviations. These were mostly related to incomplete dosing on the second cycle of the crossover. The patient numbers were #4,7,22,33,38,44, and 50.

Of the 13 patients terminated due to the suspension of the trial, 7 appeared to have data "evaluable" for cycle 1 analysis. However, only 54/67 patients were tabulated in the cycle 1 analysis of "all" patients (vide infra). As no superiority of nabilone over prochlorperazine was evident in this trial, any bias entered in the results could possibly have made nabilone look less effective. However, my own ranking of the data suggests that nabilone would have, if anything, looked better had these data been entered; i.e., N (0 vomits), P (5 vomits), N (15 vomits), N (19 vomits), N (continuous vomiting), P (continuous vomiting), P (continuous vomiting).

The evaluability of patients as a function of sequence and cancer chemotherapy is displayed in Table 3.

Table 3:
Cancer Chemotherapy By Evaluability and Sequence Group
(Sponsor's Table 1, Vol. 1.10)

<u>Cancer Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	10	11	21	17	9	26
Other combinations without cisplatin	<u>3</u>	<u>8</u>	<u>11</u>	<u>3</u>	<u>6</u>	<u>9</u>
Total	13	19	32	20	15	35

The data may also be displayed as a function of evaluable patients/dose of cisplatin (Table 4).

Table 4: Evaluable Patients per Cisplatin Dose per Sequence Group (Cycle)

<u>Cisplatin Dose</u>	<u>Seq. Gp. 1</u>	<u>Seq. Gp. 2</u>	<u>Total</u>
High (> 100 mg/m ²)	8	5	13
"Low" (≤ 100 mg/m ²)	2	6	8
None	<u>3</u>	<u>8</u>	<u>11</u>
Total	13	19	32

Statistical analysis inferred a significant group by chemotherapy interaction ($p < 0.03$). It should also be noted that the doses of cisplatin in this study are for higher than those used by Einhorn (#302), who used 20 mg/m².

The efficacy results are reported in terms of mean and standard deviation for both drugs as a function of cycle 1, cycle 2 and both cycles (Table 5).

Table 5:
Descriptive Statistics of
Daily Averages and Investigator's Global Impressions
(Sponsor's Table 1A, Vol 1.10, Appendix E, pg 277)

		<u>Daily Averages</u>			<u>Investigator's Global Impressions</u>	
		<u>Freq. of Vomits</u>	<u>Severity of Nausea</u>	<u>Food Intake</u>	<u>Efficacy</u>	<u>Adverse Effects</u>
Cycle 1						
Nabilone	Mean	10.92	1.46	1.23	2.38	0.85
	S.D.	11.72	0.88	0.44	1.26	0.90
	n	12	13	13	13	13
Compazine	Mean	5.33	1.68	1.00	2.89	0.63
	S.D.	5.22	0.89	0.75	1.59	0.60
	n	15	19	19	19	19
Cycle 2						
Nabilone	Mean	5.40	1.32	1.11	2.26	1.00
	S.D.	5.28	0.82	0.88	1.45	0.94
	n	15	19	19	19	19
Compazine	Mean	11.25	1.77	1.00	3.69	0.31
	S.D.	13.58	1.01	0.71	1.65	0.48
	n	12	13	13	13	13
Both Cycles						
Nabilone	Mean	7.85	1.38	1.16	2.31	0.94
	S.D.	8.99	0.83	0.72	1.35	0.91
	n	27	32	32	32	32
Compazine	Mean	7.96	1.72	1.00	3.22	0.50
	S.D.	10.08	0.92	0.72	1.64	0.57
	n	27	32	32	32	32

These data suggest an equivalence of nabilone to prochlorperazine with respect to vomiting and food intake. Nabilone may have a salutary effect on nausea. Investigator rated efficacy was noted slightly better for nabilone. However, overall adverse events were rated higher on nabilone. This last observation suggests the study blind may have been broken by the investigator recognizing nabilone-related side effects.

The non-parametric analysis of variance is shown in Table 6.

Table 6:
Non-Parametric Crossover Analysis on Ranks
(Sponsor's Table 2, Vol 1.10, Appendix E, pg 279)

	<u>Seq. Gp. 1</u>		<u>Seq. Gp. 2</u>		<u>Z-value</u>	<u>P-value</u>
	<u>n</u>	<u>Mean Rank</u>	<u>n</u>	<u>Mean Rank</u>		
Residual Effect						
Freq. of Vomits	13	17.27	19	15.97	0.40	.500
Sev. of Nausea	13	17.73	19	15.66	0.63	.500
Food Intake	13	17.62	19	15.74	0.58	.500
Efficacy	13	18.58	19	15.08	1.06	.291
Adverse Effects	13	14.15	19	18.11	-1.15	.250
Treatment Effect						
		(N-C)*		(C-N)*		
Freq. of Vomits	13	15.81	19	16.97	-0.33	.500
Sev. of Nausea	13	12.46	19	19.26	-2.00	.046
Food Intake	13	18.50	19	15.13	1.02	.309
Efficacy	13	12.08	19	19.53	-2.19	.029
Adverse Effects	13	20.15	19	14.00	-1.84	.066
Cycle Effect						
Freq. of Vomits	13	16.42	19	16.55	-0.02	.500
Sev. of Nausea	13	15.92	19	16.89	-0.27	.500
Food Intake	13	17.50	19	15.82	0.52	.500
Efficacy	13	14.69	19	17.74	0.89	.378
Adverse Effects	13	17.42	19	15.87	0.48	.500

*N-Nabilone, C-Compazine

Nabilone was marginally superior ($p = .046$) to prochlorperazine on the severity of nausea scale. Investigator-rated efficacy was also superior for nabilone ($p = 0.29$). Additionally, adverse effects were rated almost significantly higher ($p = .066$) for nabilone. The crossover frequency analysis is shown in Table 7. These corroborate the results in Table 6 with respect to the nausea and investigator-rated efficacy.

Table 7:
Crossover Frequency Analysis
(Table 4, Sponsor's Analysis, Vol 1.10, Appendix E, pg 281)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits					
Nabilone Better	6	5	11	.500*	.500
Same	1	5	6		
Compazine Better	6	9	15		
Total	13	19	32		
Severity of Nausea					
Nabilone Better	6	6	12	.500	.063
Same	5	12	17		
Compazine Better	2	1	3		
Total	13	19	32		
Food Intake					
Nabilone Better	4	6	10	.500	.461
Same	8	8	16		
Compazine Better	1	5	6		
Total	13	19	32		
Investigator's Global Impressions					
Efficacy					
Nabilone Better	9	9	18	.500	.054
Same	2	5	7		
Compazine Better	2	5	7		
Total	13	19	32		
Investigator's Global Impressions					
Adverse Effects					
Nabilone Better	2	4	6	.500	.229
Same	5	8	13		
Compazine Better	6	7	13		
Total	13	19	32		
Patient's Preference					
Nabilone Better	7	13	20	.500	.130
Same	1	2	3		
Compazine Better	5	4	9		
Total	13	19	32		

*From corrected Chi-square test

The frequency analysis as a function of chemotherapy group is presented in Table 8. Nabilone appears somewhat better against cisplatin-induced nausea but clearly superior against non-cisplatin regimens. Patient preference is equal in the cisplatin groups but clearly superior in the other group. It appears that nausea rating and patient preference are highly correlated. Further, investigator-rated efficacy may also be related to nausea.

Table 8
Frequency of Patients by Chemotherapy Groups
(Table 6, Sponsor's Analysis, Vol 1.10, Appendix E, pg 283)

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=21)</u>	<u>Other than Cis-Platinum (n=11)</u>	<u>Total</u>
Freq. of Vomits			
Nabilone Better	6	5	11
Same	4	2	6
Compazine Better	11	4	15
Severity of Nausea			
Nabilone Better	6	6	12
Same	12	5	17
Compazine Better	3	0	3
Food Intake			
Nabilone Better	6	4	10
Same	10	6	16
Compazine Better	5	1	6
Investigator's Global Impressions			
Efficacy			
Nabilone Better	9	9	18
Same	6	1	7
Compazine Better	6	1	7
Investigator's Global Impressions			
Adverse Effects			
Nabilone Better	5	1	6
Same	10	3	13
Compazine Better	6	7	13
Total	13	19	32
Patient's Preference			
Nabilone Better	10	10	20
Same	3	0	3
Compazine Better	8	1	9

The analysis of data from "all" cycle 1 patients is presented in Table 9. It should be noted that there are missing data for both nabilone and compazine groups with the frequency of vomiting data. The missing data may reflect patients who vomited continuously during the chemotherapy cycle. There were no significant differences observed with the efficacy variables. However, there was a trend toward superior nabilone efficacy ($p = .139$) and greater adverse effects attributed to nabilone ($p = .052$).

Table 9:
Descriptive Statistics and Test Results
Cycle 1 - All Patients
(Table 7, Sponsor's Analysis, Vol 1.10, Appendix E, pg 284)

	<u>Freq. of Vomits</u>	<u>Severity of Nausea</u>	<u>Food Intake</u>	<u>Investigator's G/ al Impressions Efficacy</u>	<u>Adverse Effects</u>
Nabilone Mean	12.58	1.82	1.00	2.67	0.93
S.D.	12.55	1.02	0.68	1.33	0.73
n	24	28	27	27	27
Median	9.00*	2.00	1.00	2.00	1.00
Compazine Mean	10.81	1.81	0.88	3.30	0.52
S.D.	13.91	0.96	0.77	1.56	0.64
n	21	27	26	27	27
Median	8.50*	2.00	1.00	4.00	0.00
Parametric Analysis					
Rank Nabilone	28.34*	28.32	28.44	24.35	31.69
Compazine	28.66*	27.67	25.50	30.65	23.31
Z-value	0.08	-0.14	-0.69	1.48	-1.95
P-value	.500	.500	.493	.139	.052

*n = 28

Investigator 302 (Lawrence Einhorn)

Patients enrolled in this study were male, female, in- and outpatients between the ages of 17 and 64. Forty-nine patients, 39 male and 10 female, were enrolled. The diagnostic frequency is given in Table 10.

Table 10: Frequency of Cancer Type in the Study Population

<u>Type</u>	<u>Number</u>	<u>(%)</u>
Testicular	32	(65)
Breast	7	(14)
Other	10	(21)

The 32 patients with testicular cancer were treated with a 5-day regimen of cisplatin (20 mg/M²). Bleomycin and vinblastine were usually administered concomitantly on the first day of the chemotherapy cycle. The seven breast cancer patients were treated with adriamycin, cyclophosphamide and 5-fluorouracil. Patients treated with cisplatin did not have to meet the criteria of two previous, consecutive vomiting episodes.

Thirty-six (36) of 49 patients enrolled were considered evaluable. Of the evaluable patients, 21 (58%) were in treatment group 1 (nabilone during 1st chemotherapy cycle) while 15 (42%) were in treatment group 2 (compazine during 1st chemotherapy cycle). The reasons for termination of the 13 patients is given in Table 11 below.

Table 11: Reasons for Early Termination

<u>Reason</u>	<u>No. of Patients</u>	<u>Patient Nos.</u>
Lost to follow up	8	15, 19, 38, 45, 47, 52, 53, 54
Protocol violation	4	2, 13, 25, 41
Adverse reaction	1	46

(Note: I assigned different termination reasons for patients 13 & 53)

Thirty (30) of the 45 patients in the trial received concomitant medications. The most common medication regimen was Colace, Flurazepam and an analgesic (Darvon, Tylenol with Codeine or Demerol). None of these medications is known to have antiemetic effects. No patient received any glucocorticoids (prednisone, dexamethasone, etc.). This last comment may be of importance as dexamethasone has recently been reported to have antiemetic efficacy in non-cisplatin chemotherapy regimens (NEJM, 9/6/84).

The evaluability of patients as a function of sequence and cancer chemotherapy is displayed in Table 12:

Table 12:
Cancer Chemotherapy By Evaluability and Sequence Group
(Table 1, Sponsor's analysis, Vol. 1.11, p. 6)

<u>Cancer Chemotherapy*</u>	<u>Evaluable</u>			<u>Evaluable</u>		
	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	13	10	23	4	7	11
Other combinations without cisplatin	<u>8</u>	<u>5</u>	<u>13</u>	<u>2</u>	<u>0</u>	<u>2</u>
Total	21	15	36	6	7	13

The frequency of cancer types was evenly distributed across sequence groups. Further, the sequence groups were comparable with respect to chemotherapy, prior chemotherapy, sex, and age.

The efficacy results are reported in terms of mean and standard deviation as a function of cycle 1, cycle 2, and both cycles. Striking group differences favoring nabilone are observed for frequency of vomits, severity of nausea, and global efficacy. Nabilone also causes more adverse effects than compazine.

Table 13:
Descriptive Statistics of Daily Averages and
Investigator's Global Impressions
(Table 2A, Sponsor's Analysis Vol 1.11, Appendix E, pg 171)

	Daily Averages			Investigator's Global Impressions	
	Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1					
Nabilone Mean	3.35	1.22	1.08	1.62	0.95
S.D.	3.98	0.83	0.78	0.74	0.59
n	21	21	21	21	21
Compazine Mean	10.06	1.99	0.79	3.00	0.40
S.D.	11.07	0.60	0.40	1.13	0.51
n	13	15	15	15	15
Cycle 2					
Nabilone Mean	3.06	1.39	0.87	1.67	1.13
S.D.	3.40	0.81	0.54	1.05	0.52
n	13	15	15	15	15
Compazine Mean	8.46	1.64	0.81	3.00	0.67
S.D.	10.51	1.00	0.67	1.18	0.66
n	21	21	21	21	21
Both Cycles					
Nabilone Mean	3.24	1.29	0.99	1.64	1.03
S.D.	3.72	0.82	0.69	0.87	0.56
n	34	36	36	36	36
Compazine Mean	9.08	1.78	0.80	3.00	0.56
S.D.	10.59	0.86	0.57	1.15	0.61
n	34	36	36	36	36

The results of the non-parametric analysis are shown in Table 14. There were no significant residual or cycle effects noted. Treatment effects favoring nabilone were observed for frequency of vomiting (day 1 $p = .004$; total average $p < .001$), severity of nausea (day 1 $p = .058$, total average $p = .004$) and food intake (total average $p = .04$). However, nabilone had a higher incidence of adverse effects ($p = .004$).

Table 14:
 Non-Parametric Crossover Analysis
 on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.11, Appendix E, pg 173)

	Mean Ranks		Z-value	P-value
	Seq. Gp. 1 (n=21)	Seq. Gp. 2 (n=15)		
Residual Effects				
Freq. of Vomits - Average	16.69	21.03	1.24	.217
- Day 1	16.40	21.43	1.43	.153
Sev. of Nausea - Average	16.71	21.00	1.22	.223
- Day 1	17.19	20.33	0.90	.369
Food Intake - Average	18.71	18.20	-0.13	.500
- Day 1	19.71	16.80	-0.80	.422
Efficacy	18.24	18.87	0.19	.500
Adverse Effects	19.45	17.17	-0.63	.500
Treatment Effect				
	(N-C)*	(C-N)*		
Freq. of Vomits - Average	13.55	25.43	3.35	<.001
- Day 1	14.29	24.40	2.86	.004
Sev. of Nausea - Average	14.21	24.50	2.90	.004
- Day 1	15.71	22.40	1.89	.058
Food Intake - Average	21.57	14.20	-2.05	.040
- Day 1	20.50	15.70	-1.33	.183
Efficacy	12.43	27.00	4.11	.001
Adverse Effects	22.81	12.47	-2.89	.004
Cycle Effect				
Freq. of Vomits - Average	19.79	16.70	-0.85	.395
- Day 1	20.12	16.23	-1.07	.282
Sev. of Nausea - Average	19.52	17.07	-0.67	.500
- Day 1	20.64	15.50	-1.43	.153
Food Intake Average	20.52	15.67	-1.35	.178
- Day 1	19.79	16.70	-0.85	.395
Efficacy	18.86	18.00	-0.22	.500
Adverse Effects	16.33	21.53	1.48	.140

*N-Nabilone, C-Compazine

The categorical analysis of the crossover data as presented in Tables 14A and 14B. In general, the analyses support the results obtained in the non-parametric analysis of the ranked data. However, the categorical analysis appears less robust.

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Table 14A
Crossover Frequency Analysis
(Table 6A, Sponsor's Analysis, Vol 1.11, Appendix E, pg 175)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u> <u>Gp. 1</u> <u>(n=21)</u>	<u>Seq.</u> <u>Gp. 2</u> <u>(n=15)</u>	<u>Total</u> <u>(n=36)</u>	<u>Cycle</u> <u>Effect</u>	<u>Treatment</u> <u>Effect</u>
Frequency of vomits - Average					
Nabilone Better	16	11	27	.500	.004
Same	1	0	1		
Compazine Better	4	4	8		
Frequency of vomits - Day 1					
Nabilone Better	10	11	21	.500	.099
Same	5	0	5		
Compazine Better	6	4	10		
Severity of Nausea - Average					
Nabilone Better	12	9	21	.500	.005
Same	6	4	10		
Compazine Better	3	2	5		
Severity of Nausea - Day 1					
Nabilone Better	4	7	11	.282	.282
Same	13	7	20		
Compazine Better	4	1	5		
Food Intake - Average					
Nabilone Better	13	5	18	.500	.150
Same	4	7	11		
Compazine Better	4	3	7		
Food Intake - Day 1					
Nabilone	17	2	9	.500	.473
Same	12	12	24		
Compazine Better	2	1	3		

The data in Table 14B corroborate the investigator's impressions in Table 13 that nabilone is more efficacious but has a higher incidence of side effects. Of particular interest, however, is the patient preference data. Patients clearly favored nabilone (29 to 6, $p < .001$)

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Table 14B
Crossover Frequency Analysis
 (Table 6B, Sponsor's Analysis, Vol 1.11, Appendix E, pg 176)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u>	<u>Seq.</u>	<u>Total</u>	<u>Cycle Effect</u>	<u>Treatment Effect</u>
	<u>Gp. 1</u>	<u>Gp. 2</u>			
	<u>(n=21)</u>	<u>(n=15)</u>	<u>(n=36)</u>		
Clinical Global Impressions					
Efficacy				.413	<.001
Nabilone Better	15	11	26		
Same	6	2	8		
Compazine Better	0	2	8		
Clinical Global Impressions					
Adverse Effects				.500	.013
Nabilone Better	3	1	4		
Same	11	4	15		
Compazine Better	7	10	17		
Patient's Preference					
Nabilone Better	17	12	29	.500	<.001
Same	0	1	1		
Compazine Better	4	2	6		

Table 15 is a summary of frequency data as a function of chemotherapy group. It is obvious that nabilone at least as effective in the cisplatin regimens as the noncisplatin regimens. Patients in the cisplatin group preferred nabilone over compazine (18 to 5).

Table 15 (Tables 7A & 8, Sponsor's Analysis, Vol 1.11, Appendix E, pg 177-78)
 Frequency of Patients by Chemotherapy Groups

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=23)</u>	<u>Other than Cis-Platinum (n=13)</u>	<u>Total</u>
Freq. of Vomits - Average			
Nabilone Better	19	8	27
Same	1	0	1
Compazine Better	3	5	8
Freq. of Vomits - Day 1			
Nabilone Better	14	7	21
Same	4	1	5
Compazine Better	5	5	10
Severity of Nausea - Average			
Nabilone Better	15	6	21
Same	7	3	10
Compazine Better	1	4	5
Severity of Nausea - Day 1			
Nabilone Better	6	5	11
Same	16	4	20
Compazine Better	1	4	5
Food Intake - Average			
Nabilone Better	12	6	18
Same	7	4	11
Compazine Better	4	3	7
Food Intake - Day 1			
Nabilone Better	3	6	9
Same	20	4	24
Compazine Better	0	3	3
Clinical Global Impressions			
Efficacy			
Nabilone Better	16	10	26
Same	7	1	8
Compazine Better	0	2	2

Table 15 (Cont'd)

<u>Treatment Comparison</u>	<u>Cis-Platinum Plus Other Combination (n=23)</u>	<u>Other than Cis-Platinum (n=13)</u>	<u>Total</u>
Clinical Global Impressions			
Adverse Effects			
Nabilone Better	2	2	4
Same	10	5	15
Compazine Better	11	6	17
Patient's Preference			
Nabilone Better	18	11	29
Same	0	1	1
Compazine Better	5	1	6

The sponsor also analyzed efficacy and safety data from all patients enrolled in cycle 1 (Table 16). Significant differences favoring nabilone were obtained with respect to day 1 vomits ($p = .002$), average daily vomits ($p = .08$), day 1 nausea severity ($p = .043$) and average daily nausea ($p = .005$). Investigator rated efficacy also favored nabilone ($p = .001$). In the cycle 1 patients, the investigators also rated nabilone as producing more severe side effects ($p = .009$). However, the rating equaled the "did not significantly interfere with patient's functioning" level.

Comments:

This investigation has demonstrated superior antiemetic and antinausea activity of nabilone compared to compazine. The rank analysis and the categorical analysis of the evaluable patients are corroborated by the all patients analysis of cycle 1. Thus, there is no apparent bias introduction into the analysis by the dropouts.

The patient preference data infer the patients favorably perceive nabilone. This is an indication that the high incidence of side effects are not considered to be overly distressing or intolerable to the majority of patients. This is an important point as most of the commonly reported side effects are of the central nervous system variety (e.g., mood changes (anxiety, depression, elation, giddiness), a "high", somnolence, vertigo, headache and blurred vision.)

One issue related to the last point is whether the nature of the side effects could have disrupted the blind for both patients and

investigators. I believe that the blind was broken for the investigator(s) if not the patients. This leads one to the question of whether or not the study is fatally flawed as a result of the blind being broken. I think not in this instance. I find the most impressive data to be the vomiting frequency. Although some expectation effect may account for a portion of the observed difference, I find it difficult to believe that expectation could have played anything but a minor role in the response. Thus, the study can be considered adequate and well-controlled, supporting the claim of an antiemetic effect of nabilone.

In the Indications section of the labeling, it would be appropriate to identify the major treatment group and the regimen, i.e., testicular cancer patients receiving cisplatin (20 mg/M²), vinblastine and bleomycin. The significance of this point is two-fold: (1) it identifies a patient population in which nabilone's efficacy was demonstrated; and (2) the combination chemotherapy of nonseminomatous testicular cancer (developed by Einhorn) appears to induce significant (@ 90%) regressions and a fairly high cure rate. Thus, nabilone would be recommended for use in one of the most successful chemotherapy regimens.

Table 16 (Table 8, Sponsor's Analysis, Vol 1.11, Appendix E, pg 179)
Cycle 1 - All Patients

	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
	Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone								
Mean	3.46	6.35	1.26	1.59	1.10	1.15	1.76	1.00
S.D.	3.93	10.27	0.85	0.97	0.78	0.82	0.88	0.58
n	26	26	27	27	27	27	25	25
Median (n=27)	3.00	3.00	1.20	2.00	1.00	1.00	2.00*	1.00*
Compazine								
Mean	8.57	12.28	1.92	2.20	0.81	0.95	2.95	0.45
S.D.	9.66	9.22	0.54	0.52	0.37	0.60	1.05	0.51
n	18	18	20	20	20	20	20	20
Median (n=20)	6.70	11.00	2.00	2.00	1.00	1.00	3.00	0.00

Non-Parametric Analysis

Mean Rank								
Nabilone	19.48	18.57	19.13	20.54	25.50	25.11	16.90	27.62
Compazine	30.10	31.32	30.57	28.67	21.97	22.50	30.63	17.22
Z-value	2.64	3.16	2.84	2.02	-0.86	-0.63	3.49	-2.63
P-value	.008	.002	.005	.043	.389	.500	.001	.009

*n=25

Investigator 306 (Rubin Bressler)

This study enrolled male and female, in- and outpatients between the ages of 23 and 78. Ten (10) patients, 4 male and female were enrolled. The study was suspended in January, 1979 due to toxicity data obtained in the one-year toxicity study in the dog. At that time, 7 evaluable patients had entered the trial.

Three patients had breast cancer and 2 had a diagnosis of lymphoma. The other 5 patients each had a different type of cancer.

Five (5) of the 10 patients received concomitant medications. The two lymphoma patients were treated with prednisone as a concomitant medication.

The evaluable patients are summarized below in Table 17 (Table 2, Sponsor's Analysis, Vol 1.11, Pg 210).

Table 17: Cancer chemotherapy - Evaluable Patients

<u>Regimen</u>	<u>Cancer</u>	<u>Frequency</u>
Adriamycin, cyclophosphamide	Breast	2
Adriamycin, dacarbazine	Connective and mesothelioma	2
Adriamycin, cyclophosphamide vincristine	Lymphoma	2
Adriamycin, mitomycin, 5-fluorouracil	Adenocarcinoma	<u>1</u>
Total		7

The results were not subjected to statistical analysis. The median number of vomits was 10 and 15 for nabilone and compazine, respectively. Average nausea ratings were 1.29 for nabilone and 1.71 for compazine. Six (6) of the 7 evaluable patients preferred nabilone.

(5) Composite analysis

Of the 126 patients entered, 75 (60%) were considered evaluable. Investigator 301 (Young) found few differences between nabilone and compazine, investigator 302 found nabilone superior to compazine with respect to emesis and nausea, and investigator 306 had a small sample size (7 patients) that had a trend towards nabilone superiority. One of the interesting aspects of this multicentered trial is the heterogeneity of cancer types and associated variables. This is

reflected in the statistical analysis which found statistically significant differences for chemotherapy, prior chemotherapy, sex, age and an investigator by evaluability interaction (the proportion of evaluable patients was different across the three investigators). In a very real sense, the only significant issue in the composite analysis is whether the negative results of investigator 301 will counter the positive results favoring nabilone found by investigator 302, causing a loss of power and/or investigator or investigator by treatment interactions.

The combined results obtained on the efficacy variables are displayed in Table 18. The frequency of vomiting data is shown both with and without the contribution of investigator 306. There are obvious trends towards reduced nausea and vomiting with nabilone. The overall means generated by the three investigators infer that nabilone may be more efficacious with less side effects.

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Table 18 (Table 3C, Sponsor's Analysis, Vol 1.10, Appendix C, pg 78)
Means
Both Cycles Combined

Drug	Investigator	n	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
			Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone	301	32	7.85a	7.85a	1.38	1.38	1.16	1.16	2.31	0.94
	302	32	3.24b	6.47b	1.29	1.58	0.99	1.06	1.64	1.03
	306	7	7.00c	7.00c	1.29	1.29	0.86	0.86	2.14	1.00
Composite		75 (68)	5.43d (5.28)e	7.07d (7.08)e	1.33	1.47	1.05	1.08	1.97	0.99
Compazine	301	32	7.96a	7.96a	1.72	1.72	1.00	1.00	3.22	0.50
	302	36	9.08b	12.59b	1.78	1.94	0.80	0.86	3.00	0.56
	306	7	20.73c	20.33c	1.71	1.71	0.71	0.71	3.14	0.57
Composite		75	9.64d	11.42d	1.75	2.83	0.88	0.91	3.11	0.53

n=27, b_n=34, c_m=6. d_m=67. e_n=61

() = without investigator 306

The results of the composite crossover analysis of variance on the ranked data. When corrected for an investigator by residual interaction which resulted in dropping the frequency of vomiting data from investigator 306, and corrected for an investigator by treatment interaction (by determination of a new error mean square term using the appropriate investigator by treatment sum of squares), significant differences favoring nabilone were evident with respect to all subject-rated efficacy variables. The investigator-rated variables showed a difference in adverse event severity, favoring compazine.

Table 19:
Crossover Analysis of Variance on Ranks
(Table 5, Sponsor's Analysis, Vol 1.10, Appendix C, pg 82)

Treatment Effect	Investigator		Residual		Inv. x Residual		Error S.S.C
	S.S.a	P	S.S.b	P	S.S.a	P	
Freq. of Vomits - Average	1436	.215	1182	.112	2625	.063	31518
	- Day 1	610	1034	.141	2904	.050	32096
Sev. of Nausea - Average	182	.500	460	.330	1518	.211	32899
	- Day 1	791	309	.409	1046	.316	30850
Food Intake - Average	1408	.228	197	.500	725	.463	32124
	- Day 1	996	73	.500	751	.434	30678
Efficacy	3029	.035	1394	.076	1207	.253	29718
	Adverse Effects	608	201	.497	802	.399	29694
Removing INV = 306							
Freq. of Vomits - Average	657b	.198	42	.500	563b	.233	24811d
	- Day 1	54b	142	.500	601b	.222	25333d
Treatment Effect	Investigator		Treatment		Inv. x Treatment		Error S.S.C
	S.S.a	P	S.S.b	P	S.S.a	P	
Freq. of Vomits* - Average	30b	.500	2590	.007	1620	.032	21643
	- Day 1	211b	1834	.027	1182b	.073	22777
Sev. of Nausea - Average	233	.500	2774	.007	305	.500	24770
	- Day 1	617	1907	.024	9	.500	24544
Food Intake - Average	980	.314	2764	.012	596	.493	28714
	- Day 1	902	2141	.018	458	.500	25267
Efficacy	241	.500	5083	.001	282	.500	23323
	Adverse Effects	1090	3448	.003	193	.500	25439

dd.f.f.=2, bd.f.f.=1, Cd.f.f.=69, dd.f.f.=64

*Omitting Investigator 306

Analysis of all cycle 1 patients showed an investigator effect and significant (day 1) and nearly significant (p<.10) investigator by treatment effects for day 1 and average frequency of vomiting, respectively. I believe the statistical analysis of the cycle 1 group is showing that the results across investigators are not comparable on the frequency of vomiting data. Further, cycle 1 data are insensitive to treatment differences.

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Table 20:
 Cycle 1 - All Patients
 Analysis of Variance on the Ranks
 (Table 8, Sponsor's Analysis, Vol 1.10, Appendix C, pg 86)

Treatment Effect	Investigator		Treatment		Inv. x Treatment		Error	
	S.S.A	P	S.S.B	P	S.S.A	P	S.S.C	d.f.
Freq. of Vomits- Average	7747	.020	8	.500	4457	.102	101242	106
- Day 1	1958	.374	106	.500	6260	.046	104444	106
Sev. of Nausea - Average	2913	.214	366	.500	3573	.152	97880	105
- Day 1	197	.500	167	.500	2869	.204	93370	105
Food Intake - Average	95	.500	51	.500	472	.500	93099	103
- Day 1	540	.500	9	.500	485	.500	85287	103
Efficacy	3975	.088	3244	.047	2170	.262	81528	102
Adverse Effects	508	.500	7284	.002	387	.500	74065	102

ad.f.=2, bd.f.=1

The analysis of patient preference showed that for both evaluable patients (evaluable plus unevaluable) showed that patients in both groups preferred nablone (p < .001), both groups.

Conclusions:

The results obtained in this study demonstrate the antiemetic superiority of nablone over compazine in patients receiving cancer chemotherapy. The effect was most notable in the Einhorn study (#302) in which a fairly homogenous group of patients was studied. The labeling should identify that nablone is effective against nausea and vomiting produced by cisplatin (20 mg/m²), vinblastine and bleomycin in testicular cancer patients.

In the discussion of the Einhorn data, I noted that I believed the blind could not have been maintained but that this was not a serious flaw in judging the results. My comments are also applicable to the overall conclusions inasmuch as the Einhorn data are the major component of the data demonstrating nablone's antiemetic superiority over compazine.

b. Protocol #7

Investigator (Rubin Bressler)

This study was conducted in cancer patients from the University of Arizona Medical Center and the Tucson Veterans Administration Hospital. This was a double-blind, randomized crossover study comparing the safety and efficacy of nabilone versus compazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents in two consecutive chemotherapy cycles. Patients were randomly assigned to receive either nabilone or prochlorperazine during the first cycle of chemotherapy and the other drug during the second cycle. The study drug was to be administered throughout the chemotherapy cycle, a 1 to 5-day treatment period. Chemotherapy cycles were usually given 3 to 6 weeks apart.

Administration of the test drug began the evening before chemotherapy. Dosing was continued 1/2 hour before chemotherapy and 1/2 hour before meals throughout the course of chemotherapy. Dosing with nabilone varied and ranged from 1 to 6 mg/day. Compazine doses ranged from 10 to 30 mg per day.

Criteria for study participation were that cancer patients, aged 17 to 70, of either sex could participate. These patients had to have experienced severe nausea and vomiting with previous courses of chemotherapy. Pregnant women and patients with severe atherosclerotic vascular disease were ineligible.

Efficacy was determined by three patient-related criteria every 24 hours of chemotherapy. The criteria were the frequency of vomiting, the severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual amount, more than usual). In addition to the sponsor's analysis, the investigator performed an apparent post-hoc analysis on the quality of the antiemetic response in evaluable subjects. Responses were scored as complete if no nausea or vomiting were recorded, partial if a 50% or greater reduction in nausea and vomiting was achieved, and "no response" if a less than 50% reduction in nausea and vomiting were recorded.

Safety evaluation included a medical history, hematology, and SMA 12/60 completed on each patient prior to each period of study drug. The test battery was repeated prior to the next chemotherapy and following each patient's termination. Adverse reactions were recorded by patients; investigator(s) recorded on a separate report from his/their evaluation of adverse experiences and his/their opinion as to the relationship to study drug.

The primary diagnosis for the study was nausea and vomiting associated with cancer chemotherapy. Secondary diagnosis was any type of cancer being treated by a chemotherapeutic agent(s) known to cause nausea and vomiting. Each patient's age, sex, intercurrent illnesses and concomitant medications were also recorded.

Patients were considered evaluable if they completed at least one day on each study drug and no "protocol violations" occurred on these days in either cycle. The lesser of the two numbers; i.e., evaluable days in cycle 1 versus evaluable days in cycle 2, was used in the analysis.

Efficacy parameters were considered independently when assigning evaluability; i.e., missing data from one parameter did not negate an evaluation of the other parameters.

Protocol violations were defined as any event listed below:

- (1) A second antiemetic was given other than the study drug assigned by the randomization schedule;
- (2) Study drug was not administered concomitantly with chemotherapy;
- (3) Specific dose of antiemetic, as called for by the study protocol, was not given 30 minutes prior to chemotherapy;
- (4) A different chemotherapy regimen was instituted in the second chemotherapy cycle; and
- (5) Smoking marijuana on either cycle.

Statistical Analysis

The sequence groups were analyzed with respect to evaluability, chemotherapy, prior chemotherapy, sex and age and interaction effects (group x sex x evaluability).

The data analysis was essentially that described in protocol 20. A non-parametric analysis of ranks was performed. Data were analyzed for residual effects before both cycles were combined. Categorical analysis was performed on the variables (nabilone better, same, compazine better) with respect to cycle and treatment effects. An analysis of all patients in cycle 1 was performed.

Blood pressure changes (recumbent and standing) were analyzed for direction of change within drug therapy and magnitude of change across therapy.

Patient characteristics

Forty-three (43) patients enrolled in the study; 18 were male and 25 female. Twenty-nine (29) patients aged 17 to 70 were considered evaluable for the efficacy analysis. The type of cancers found in the population are listed below in Table 21.

Table 21:
Frequency of Cancer Type in Study Population

Type	Number	(%)
Hodgkin's	13	(30)
Non-Hodgkin's lymphoma	8	(19)
Breast	8	(19)
Other*	14	(32)

*These occurred with a frequency of 3 or less

The most frequent treatment used was bleomycin, nitrogen mustard, procarbazine and vincristine in patients with Hodgkin's disease. The chemotherapy by evaluability and sequence groups is given in Table 22.

Table 22
Cancer Chemotherapy By Evaluability and Sequence Group
(Table 1, Sponsor's Analysis, Vol. 1.15, pg 13)

Cancer Chemotherapy	Evaluable			Unevaluable		
	Seq. Gp. 1	Seq. Gp. 2	Total	Seq. Gp. 1	Seq. Gp. 2	Total
Cisplatin + other chemotherapies	3	1	4	2	0	2
Adriamycin + other chemotherapies*	5	6	11	3	3	6
Other than cisplatin or Adriamycin	<u>3</u>	<u>11</u>	<u>14</u>	<u>5</u>	<u>1</u>	<u>6</u>
Total	11	18	29	10	4	14

*Not including cisplatin

As can be seen by inspection, the statistical analysis verified a group by evaluability interaction. Further, the sequence by chemotherapy by evaluability interaction was statistically significant ($p = .031$).

The mean and standard deviations of the efficacy parameters (day 1 and average) are displayed as individual cycle data and combined data in Table 23. Further, the standard deviations are approximately equal to the means. This indicates a high degree of variability in the antiemetic response to both drugs. There is also an indication of a cycle effect as vomiting in both treatment groups appears more frequent in the second cycle.

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**Table 23:
Descriptive Statistics
Daily Averages**

(Table 2, Sponsor's Analysis, Vol 1.15, Appendix E, pg 147)
Daily Averages

		Freq. of Vomits		Severity of Nausea		Food Intake-	
		Average	Day 1	Average	Day 1	Average	Day 1
Cycle 1							
Nabilone	Mean	4.70	4.90	1.41	1.73	1.07	1.00
	S.D.	5.38	5.30	1.11	1.27	0.71	0.77
	n	10	10	11	11	11	11
Compazine	Mean	7.57	8.24	1.71	1.83	1.08	1.06
	S.D.	11.13	11.15	1.21	1.34	0.75	0.73
	n	17	17	18	18	18	18
Cycle 2							
Nabilone	Mean	5.88	7.35	1.52	1.78	1.19	1.11
	S.D.	7.22	7.77	1.19	1.31	0.55	0.68
	n	17	17	18	18	18	18
Compazine	Mean	11.70	13.10	1.82	2.18	0.80	0.55
	S.D.	9.71	11.00	1.05	1.08	0.53	0.52
	n	10	10	11	11	11	11
Both cycles							
Nabilone	Mean	5.44	6.44	1.48	1.76	1.15	1.07
	S.D.	6.51	6.95	1.15	1.27	0.60	0.70
	n	27	27	29	29	29	29
Compazine	Mean	9.10	10.04	1.75	1.97	0.97	0.86
	S.D.	10.63	11.14	1.13	1.24	0.68	0.69
	n	27	27	29	29	27	27

The results of the non-parametric crossover analysis are displayed in Table 24. There is a trend towards antiemetic superiority ($p = .10$) with nabilone. The differences between the two drugs are not as great as the difference in vomiting between cycles. Day 1 vomits were significantly different ($p = .031$) with respect to cycle whereas average vomits were marginally ($p = .058$) different between cycles. There was no residual effect observed on any of the three efficacy parameters.

Table 24:
 Non-Parametric Crossover Analysis on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.15, Appendix E, pg 149)

	Seq. Gp. 1		Seq. Gp. 2		Z-value	P-value
	n	Mean Rank	n	Mean Rank		
Residual Effects						
Freq. of Vomits- Average	10	14.40	18	14.56	-0.02	.500
- Day 1	10	14.10	18	14.72	-0.17	.500
Sev. of Nausea - Average	11	14.82	18	15.11	0.07	.500
- Day 1	11	15.59	18	14.64	0.31	.500
Food Intake - Average	11	13.64	18	15.83	-0.65	.500
- Day 1	11	12.27	18	16.67	-1.33	.185
Treatment Effect						
		(N-C)*		(C-N)*		
Freq. of Vomits- Average	10	11.10	18	16.39	-1.61	.108
- Day 1	10	11.45	18	16.90	1.44	.150
Sev. of Nausea - Average	11	12.23	18	16.69	1.35	.178
- Day 1	11	12.73	18	16.39	1.10	.271
Food Intake - Average	11	17.82	18	13.28	1.42	.157
- Day 1	11	18.05	18	13.14	1.53	.127
Cycle Effect						
Freq. of Vomits- Average	10	10.50	18	16.72	-1.89	.058
- Day 1	10	9.95	18	17.03	-2.16	.031
Sev. of Nausea - Average	11	15.09	18	14.94	0.07	.500
- Day 1	11	13.82	18	15.72	-0.56	.500
Food Intake Average	11	15.55	18	14.67	0.29	.500
- Day 1	11	16.95	18	13.81	0.99	.323

*N=Nabilone, C=Compazine

The crossover frequency analysis (Table 25) showed trends toward cycle effects for day 1 vomits (p = .119) and average vomits (p = .193). No statistically significant differences between nabilone and compazine were found in the analysis. Thus, using this type of analysis, no superiority of nabilone over compazine was demonstrated.

Table 25:
Crossover Frequency Analysis
(Table 4, Sponsor's Analysis, Vol 1.10, Appendix E, pg 281)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits - Average					
Nabilone Better	6	8	14	.193	.297
Same	3	1	4		
Compazine Better	<u>1</u>	<u>9</u>	<u>10</u>		
Total	10	18	28		
Freq. of vomits - Day 1					
Nabilone Better	6	7	13	.119	.436
Same	3	1	4		
Compazine Better	<u>1</u>	<u>10</u>	<u>11</u>		
Total	10	18	28		
Severity of Nausea - Average					
Nabilone Better	5	8	13	.500	.413
Same	3	6	9		
Compazine Better	<u>3</u>	<u>4</u>	<u>7</u>		
Total	11	18	29		
Severity of Nausea - Day 1					
Nabilone Better	5	5	10	.500	.500
Same	4	9	13		
Compazine Better	<u>2</u>	<u>4</u>	<u>6</u>		
Total	11	18	29		
Food Intake - Average					
Nabilone Better	4	8	12	.500	.402
Same	5	6	11		
Compazine Better	<u>2</u>	<u>4</u>	<u>6</u>		
Total	11	18	29		
Food Intake - Day 1					
Nabilone Better	5	6	11	.500	.500
Same	5	8	13		
Compazine Better	<u>1</u>	<u>4</u>	<u>5</u>		
Total	11	18	29		

The cycle 1 analysis of all patients failed to show any statistically significant differences between nabilone and compazine on any of the efficacy parameters (data not shown). Thus, on these measures, antiemetic

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superiority was not demonstrated. However, the investigators performed a post-hoc analysis on the quality of the antiemetic response. The results of this study are displayed in Table 26 (Table 14), Sponsor's Analysis, Vol. 1.15, pg 28).

Table 26:
Quality of Antiemetic Response in 33 Evaluable Patients

<u>Drug</u>	<u>Response</u>		
	<u>Complete</u>	<u>Partial</u>	<u>None</u>
Nabilone	9 (27%)	21 (64%)	3 (5%)
Compazine	0	11 (33%)	22 (56%)

The investigators applied McNemar's test to test the association of drug with response. They also compiled vomiting data (61 + risk days) which they evaluated by the sign test. The results of combined complete and partial responses clearly favor nabilone (p .001). The results of the complete response category also favor nabilone (p .005). The results of the sign test showed a statistically significant reduction in the number of days with greater vomiting frequency (p = 0.05, sign test).

Comment:

Although these data are a very interesting analysis, there may be a bias involved due to dropouts (8/13 dropouts were due to intolerable or unacceptable side effects due to nabilone) or scoring criteria (several of the partial responses to compazine were nearly complete). At any rate, we were not supplied with baseline (previous) vomiting data. Thus, it is not possible to recalculate the results or perform other non-parametric analyses of the data. The problem with accepting the results of the sign test is that a bias may have occurred due to the 8 dropouts.

Conclusion:

The results of this study suggest a trend toward antiemetic superiority of nabilone over compazine. However, as statistically significant superiority was not demonstrated, this study does not support the efficacy of nabilone.

c. Protocol #9

Investigator (Lawrence Einhorn)

This study was conducted in cancer patients from the University of Indiana Medical Center. This study was a double-blind, randomized crossover study comparing the safety and effectiveness of nabilone versus compazine in the treatment of emesis and nausea produced by cancer chemotherapeutic agents

in two consecutive chemotherapy cycles. Patients were randomly assigned to receive either nabilone or compazine during the first cycle and the 4 other drugs during the second cycle. The study drug was administered concomitant with chemotherapy throughout the 1- to 5-day chemotherapy cycle. Chemotherapy cycles were usually 2 to 4 weeks apart.

Administration of the test drug to the first 60 patients began 30 minutes before chemotherapy. The protocol was amended to allow dosing to begin the evening before chemotherapy. Nabilone was administered as a 1 mg capsule and compazine was administered as a 5 mg capsule. The schedule of administration was 2 mg nabilone, q. 6h., p.r.n., or 10 mg compazine, q. 6h., p.r.n. Capsules were identical in appearance to maintain the double-blind nature of the study.

Criteria for participation were that patients had to be receiving chemotherapy known to cause nausea and vomiting. Informed consent was obtained from each patient. Pregnant women and patients with cardiac disease were excluded from the protocol.

Efficacy was determined on the patient-rated variables per 24-hour period of chemotherapy. Patients recorded the number of vomiting episodes, the severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual amount, more than usual).

Safety data included a history and physical examination prior to each course of chemotherapy. Laboratory testing included hematology and blood chemistry (SMA 12/60) before and after each cycle. Blood pressure and heart rates were obtained in patients after lying, sitting and standing. Determinations were performed every 6 hours following study drug administration and for 12 hours after study completion. Adverse reactions were noted by patients and the investigators. The investigator rendered an opinion as to the cause of the reaction.

The primary diagnosis of the patients was nausea and vomiting due to cancer chemotherapy. The secondary diagnosis was the type of cancer being treated by cancer chemotherapeutic agents known to cause nausea and vomiting. Each patient's sex, age, intercurrent illnesses and concomitant medications were also recorded.

Patients were considered evaluable if they completed at least one day of study drug administration on each cycle. The total number of evaluable days per cycle were the number of consecutive days of test drug administration in which no protocol violations occurred. The lesser of the two numbers of evaluable days per cycle was used in the efficacy analysis.

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Efficacy parameters were considered independently when considering evaluability of data.

Protocol violations were the same as those used in Protocol 7, and are listed below:

- (1) A second antiemetic was given other than the study drug assigned by the randomization schedule;
- (2) Study drug was not administered concomitantly with chemotherapy;
- (3) Specific dose of antiemetic, as called for by the study protocol, was not given 30 minutes prior to chemotherapy;
- (4) A different chemotherapy regimen was instituted in the second chemotherapy cycle; and
- (5) Smoking marijuana on either cycle.

Statistical Analysis

The sequence groups were analyzed with respect to evaluability, cancer diagnosis, chemotherapy, prior chemotherapy, sex, age and interaction effects.

Data analysis was essentially that described in Protocol 20. A non-parametric analysis of ranks was performed for each cycle and both cycles combined (after testing for a residual effect and finding none). The crossover frequency analysis compared the treatment and tested for cycle effects. Further, an analysis of all patients in cycle 1 was performed.

Blood pressure changes were analyzed for statistical significance for direction of change within drug therapy and magnitude of change across drugs.

Patient Characteristics

Ninety-eight (98) patients (83 male, 15 female) aged 15 to 74 were enrolled in the trial. Eighty-three (83) patients completed the crossover. The type of cancers found in the study population are listed below in Table 27.

Table 27:
Frequency of Cancer Type By Cycle in Protocol 9

<u>Type</u>	<u>Number</u>	<u>(%)</u>	<u>Cycle 1 evaluable</u>	<u>Cycle 2 evaluable</u>
Testicular	76 (78)		33	35
Ovarian	5	(5)	1	2
Bladder	5	(4)	1	2
Hodgkin's	4	(4)	0	2
Other	9	(9)	4	3

The most frequent chemotherapy regimen was 5 days of cisplatin (20 mg/M²) 1 or 2 days of bleomycin, vinblastine or adriamycin in the treatment of testicular cancer. Sixty-eight (68) of 83 completers had testicular cancer. Thus, the result will mostly reflect what happened in this population. The statistical analysis of patient and cancer treatment variables bears this out; i.e., the sequence (cycle) groups were comparable with respect to chemotherapy, previous chemotherapy, sex and age.

Fifteen (15) patients failed to complete the crossover. Of these, 8 patients were terminated early according to Table 28. Further, 7 patients (#12, 18, 26, 36, 58, 67, and 91) were considered unevaluable due to protocol violations. Patient #44 terminated after 1 dose of nabilone in cycle 2 but was counted in the efficacy analysis.

Table 28: Reasons for Early Terminations
(Table 10, Sponsor's Analysis, Vol. 1.14, pg 25)

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse experience (nabilone)	4	11, 14, 15, 44
Lack of efficacy (nabilone)	1	29
Lack of efficacy (nabilone and prochlorperazine)	2	65
Physician decision	2	5, 27
Complicating decisions	1	1

The tabulation of patient doses of test drug by day of chemotherapy is given in Table 29. Sixty-eight (68) of 94 (72%) of those receiving nabilone on day 1 continued with nabilone on day 5. Seventy (70) of 91 (77%) of those receiving compazine on day 1 were still receiving it on day 5. In both treatment groups there is a shift towards lower dosage on days 3 through 5 of the chemotherapy cycle.

Table 29 (Table 11, Sponsor's Analysis, Vol 1.14, pg 28)
 Frequency of Patients by Total Daily Dose
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	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Nabilone							
1 or 2 mg	25	21	18	24	27	27	
3 or 4 mg	8	30	28	20	19	14	
Greater than 4 mg	2	43	38	33	28	27	
Total	35	94	84	77	74	68	
Prochlorperazine							
1 or 2 mg	20	19	18	25	25	31	
15 or 20 mg	9	35	22	15	14	14	
25 or 30 mg	0	12	20	15	12	14	
Greater than 30 mg	2	25	25	23	25	11	
Total	31	91	85	78	76	70	

Efficacy data are tabulated in terms of means and standard deviations in Table 30. Visual inspection of the data suggest both treatment and cycle-related effects for the 3 parameters. Combined means from both cycles suggest a superior antiemetic effect for nabilone.

Table 30:
Descriptive Statistics
Daily Averages
(Table 2, Sponsor's Analysis, Vol 1.14, Appendix E, pg 371)

		Daily Averages					
		Freq. of Vomits		Severity of Nausea		Food Intake	
		Average	Day 1	Average	Day 1	Average	Day 1
Cycle 1							
Nabilone	Mean	1.96	5.23	1.29	1.82	1.20	1.21
	S.D.	1.80	5.65	0.89	1.19	0.57	0.66
	n	39	39	39	39	38	38
Compazine	Mean	6.50	9.79	1.70	2.12	0.85	0.86
	S.D.	7.62	8.76	0.90	0.99	0.52	0.68
	n	42	42	42	42	43	43
Cycle 2							
Nabilone	Mean	5.59	9.55	1.43	2.24	0.95	0.91
	S.D.	7.65	8.06	0.95	0.82	0.59	0.75
	n	42	42	42	42	43	43
Compazine	Mean	6.93	11.46	2.07	2.51	0.83	0.97
	S.D.	6.11	8.50	0.86	0.85	0.51	0.64
	n	39	39	39	39	38	38
Both cycles							
Nabilone	Mean	3.84	7.47	1.36	2.04	1.06	1.05
	S.D.	5.90	7.29	0.92	1.03	0.59	0.72
	n	81	81	81	81	81	81
Compazine	Mean	6.71	10.59	1.88	2.31	0.84	0.91
	S.D.	6.89	8.63	0.90	0.94	0.52	0.66
	n	81	81	81	81	81	81

The non-parametric analysis of the ranked data is presented in Table 31. There were no residual effects noted on any of the efficacy parameters. There were treatment-related effects favoring nabilone for day 1 ($p < .001$) and average vomiting frequency ($p < .001$), nausea severity day 1 ($p = .074$) and average ($p < .001$), and average food intake ($p < .001$). Additionally statistically significant cycle effects were observed for day 1 ($p = .006$) and average vomiting frequency ($p = .004$), and severity of nausea day 1 ($p = .009$) and average ($p = .05$).

Table 31:
Non-Parametric Crossover Analysis
(Table 4, Sponsor's Analysis, Vol 1.14, Appendix E, pg 373)

	Seq. Gp. 1		Seq. Gp. 2		Z-value	P-value
	n	Mean Rank	n	Mean Rank		
Residual Effects						
Freq. of Vomits- Average	39	40.97	44	42.91	-0.36	.500
- Day 1	39	39.60	44	44.13	-0.85	.396
Sev. of Nausea - Average	39	43.42	42	38.76	0.89	.372
- Day 1	39	41.44	42	40.60	0.17	.500
Food Intake - Average	38	43.45	43	38.83	-0.88	.376
- Day 1	38	45.33	43	37.17	-1.56	.118
Treatment Effect						
		(N-C) ^c		(C-N) ^a		
Freq. of Vomits- Average	39	16.60	44	55.65	-5.47	<.001
- Day 1	39	32.27	44	50.63	3.46	<.001
Sev. of Nausea - Average	39	28.21	42	52.88	4.71	<.001
- Day 1	39	36.14	42	45.51	1.79	.074
Food Intake - Average	38	51.86	43	31.41	3.91	<.001
- Day 1	38	45.13	43	37.35	1.49	.136
Cycle Effect						
Freq. of Vomits- Average	39	33.82	44	49.25	-2.91	.004
- Day 1	39	34.27	44	48.85	-2.75	.006
Sev. of Nausea - Average	39	35.67	42	45.95	-1.96	.050
- Day 1	39	33.91	42	47.58	-2.61	.009
Food Intake Average	38	45.13	43	37.35	1.49	.136
- Day 1	38	43.05	43	39.19	0.74	.458

*N=Nabilone, C=Compazine

The results of the categorical analysis are listed in Table 32. Treatment effects favoring nabilone were observed on day 1 vomits (p = .002), average vomits (p < .001), average severity of nausea (p < .001) and average food intake (p < .001). Cycle effects were also noted for day 1 vomits (p = .002) average frequency of vomiting (p < .001) and severity of nausea (p = .034). These results corroborate the results of the non-parametric crossover analysis (Table 31).

Table 31:
Crossover Frequency Analysis
(Table 6: Sponsor's Analysis, Vol 1.14, Appendix E, pg 375)

Treatment Comparison	Frequency of Patients			P-Value	
	Seq. Gp. 1	Seq. Gp. 2	Total	Cycle Effect	Treatment Effect
Freq. of vomits - Average					
Nabilone Better	37	25	62	<.001	<.001
Same	1	6	7		
Compazine Better	<u>1</u>	<u>13</u>	<u>14</u>		
Total	39	44	83		
Freq. of vomits - Day 1					
Nabilone Better	32	19	51	.002*	.002*
Same	2	6	8		
Compazine Better	<u>5</u>	<u>19</u>	<u>24</u>		
Total	39	44	83		
Severity of Nausea - Average					
Nabilone Better	30	22	52	.493	<.001*
Same	3	12	15		
Compazine Better	<u>6</u>	<u>8</u>	<u>14</u>		
Total	39	42	81		
Severity of Nausea - Day 1					
Nabilone Better	18	10	28	.034*	.208*
Same	16	19	35		
Compazine Better	<u>5</u>	<u>13</u>	<u>18</u>		
Total	39	42	81		
Food Intake - Average					
Nabilone Better	21	19	40	.500	<.001
Same	13	17	30		
Compazine Better	<u>4</u>	<u>7</u>	<u>11</u>		
Total	38	43	81		
Food Intake - Day 1					
Nabilone Better	12	12	24	.500*	.167*
Same	21	22	43		
Compazine Better	<u>5</u>	<u>9</u>	<u>14</u>		
Total	38	43	81		

*From corrected chi-square test

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The results of the "all patients" analysis of the first chemotherapy cycle are presented in Table 33. Statistically significant differences, favoring nabilone, are observed with all three efficacy parameters. Specifically, day 1 and average vomiting frequency favor nabilone, $p = .038$ and $p = .005$, respectively, as does food intake (average, $p = .022$). Average nausea severity exhibited a trend towards significance ($p = .09$) which favored nabilone.

Table 33:
Descriptive Statistics and Test Results
Cycle 1 - All Patients
(Table 8, Sponsor's Analysis, Vol 1.14, Appendix E, pg 377)

		Freq. of Vomits		Severity of Nausea		Food Intake-	
		Average	Day 1	Average	Day 1	Average	Day 1
Nabilone	Mean	3.11	6.91	1.33	1.89	1.13	1.14
	S.D.	6.12	8.72	0.95	1.20	0.63	0.71
	n	44	44	44	44	43	43
	Median	1.90	4.50	1.37	2.00	1.00	1.00
Compazine	Mean	6.02	9.50	1.64	2.12	0.85	0.84
	S.D.	7.50	8.76	0.84	0.98	0.48	0.68
	n	43	43	43	43	44	44
	Median	4.00*	8.00*	1.60	2.00	1.00	1.00

Non-Parametric Analysis

Mean Rank							
Nabilone	37.14	39.24	39.47	42.18	50.24	48.76	
Compazine	52.69	50.63	48.64	45.86	37.90	39.35	
Z-value	-2.84	-2.08	1.70	0.68	2.28	1.74	
P-value	.005	.038	.090	.494	.022	.082	

*n = 45

Conclusions:

In this study, nabilone appears to be a superior antiemetic to prochlorperazine. As the majority of the patients (82%) were testicular cancer patients receiving cisplatin or adriamycin, this fact could be highlighted in the Indications section of the labeling.

There is one issue regarding replication which deserves some discussion. Usually one likes to see replication of drug effect by different investigators in the same or similar study population. Both "positive" studies favoring nabilone over compazine were performed by the same investigator in essentially the same (cancer type) population. Although this is less desirable than replication by different investigators, the replication of an antiemetic superiority over compazine against cisplatin combination regimes (a potent emetic stimulus) is strongly persuasive of antiemetic efficacy of nabilone.

d. Protocol 28

Background:

This was a multicentered, double-blind, randomized, placebo-controlled crossover study comparing the effects of nabilone versus placebo in the treatment of nausea and vomiting associated with cyclic cancer chemotherapy. Six investigators participated in the trial. The sponsor analyzed the results of the individual investigators as well as the composite results. At the time of the NDA submission, three investigators [(#002 - Einhorn), (#005 - Levitt) and (#006 - Gunnell)] had studies in progress. Data were analyzed from these studies on results obtained prior to NDA submission. To my knowledge, there were no subsequent amendments which supplied further data at study completion with reanalysis of all data.

Study design

This was a double-blind, randomized, placebo-controlled, two-period crossover study of the antiemetic effect of nabilone in cancer patients undergoing consecutive cycles of chemotherapy known to produce nausea and vomiting. Patients received nabilone or placebo during the first cycle of chemotherapy and were switched to the other drug treatment for the second cycle of chemotherapy. The study drug was administered concomitantly with chemotherapy, generally a 1- to 5-day treatment course. Chemotherapy cycles were usually 3 to 6 weeks apart.

Study drug administration began the evening before chemotherapy. The study drug was to be administered 1 to 3 hours before initiation of chemotherapy and then once in the evening. The dose of nabilone for each administration was 2 mg. Placebo doses were administered in identical appearing capsules.

Criteria for study participation were that male or female, inpatients or outpatients had to be at least 16 years old, give written informed consent and be given a treatment regimen that was not expected to change over two consecutive chemotherapy courses. Eligible patients could be excluded on

the basis of any of the following factors: (1) receiving high dose cisplatin (100 mg/M²/day); (2) pregnancy; (3) no contraceptive use (fertile women); (4) clinically significant cardiovascular, hepatic, renal or CNS disease; (5) psychosis; (6) progressive disease of the eye(s); (7) weight of less than 45 kg; (8) alcohol or drug addiction; and (9) use of other psychotropic drugs, including marijuana, during the study.

Patients were to be randomized to a treatment group (nabilone or placebo) at time of admission. Assignment was stratified to insure a balanced distribution of patients who had previous chemotherapy and those who were beginning chemotherapy.

Efficacy criteria were rated by patients on a 24-hour basis. The patient-rated variables were vomiting frequency, severity of nausea (none, mild, moderate, severe) and food intake (none, less than usual, usual, more than usual). Patients were also asked to rate their preference for the antiemetic response in cycle 1 or cycle 2. Investigators rated global efficacy (very good, good, fair, poor, very poor) and adverse effects (none, did not interfere with patient's functioning, significantly interfered with patient's functioning, outweighed therapeutic effect).

Safety parameters included the taking of a medical history, physical examination at admission, and a physical examination after the study was completed. Clinical laboratory parameters (hematology - hemoglobin, hematocrit, reticulocyte, WBC, platelet count, and differential; SMA 12/60 and urinalysis) were determined within one week prior to cycle 1 and then within two weeks after study completion or discontinuation. Blood pressure and pulse rates were to be obtained within the week prior to each course of chemotherapy and after the second cycle had been completed or the study drug discontinued. Patients were to be monitored for postural hypotension 3 to 4 hours after the morning dose of study medication, where feasible. Recumbent and standing blood pressures were to be determined.

Adverse reactions volunteered by the patient or noted by an observer were to be recorded. The investigator was asked to rate the severity of the reaction as well as determine whether it was study drug-related.

To be considered evaluable for the crossover, patients had to complete at least one "evaluable" day on each cycle. Evaluable days were defined as the number of consecutive treatment days in which study drug and chemotherapy were administered and no "protocol violations" occurred. As in the other protocols, efficacy criteria were considered independently; i.e., missing data on one variable did not compromise the use of the data on other variables.

Three conditions were considered protocol violations:

1. administration of a second antiemetic, including marijuana, not assigned in the randomization schedule;
2. the specific dose of antiemetic was not administered 1-3 hours prior to chemotherapy; and
3. alteration of the chemotherapy regimen in cycle 2 of the protocol.

Statistical analysis

The sponsor analyzed several factors across investigators for comparability. The following analyses were performed with respect to sequence groups: cancer type, chemotherapy, previous chemotherapy, sex and age. In the individual analyses of each investigator, sequence groups (cycles) were compared with respect to evaluability, chemotherapy, previous chemotherapy, sex and age.

Efficacy data were tabulated with respect to mean and medians on the parameters. Individual and composite results are presented. The sponsor then performed a composite analysis incorporating both cycles using data from all investigators. Data were combined only after testing for a residual (carryover) effect. An analysis of variance was performed on the ranked data. A separate cycle analysis was also performed on the individual and composite data. Finally, a composite cycle 1 analysis on all patients was performed.

Blood pressure data were analyzed for the number of patients demonstrating changes (increase vs. decrease) in systolic and diastolic pressure within treatments on both an investigator and a composite basis. Data were also analyzed for the magnitude of pressor and depressor effects between treatments on both an investigator and a composite basis. The between treatment comparison was made on patients completing both cycles. The data were categorized as to whether the nabilone decrease was greater than the placebo decrease, the magnitude of the decrease was equal, or the placebo decrease was greater than the nabilone decrease. A Chi-Square analysis of the categorical data was then performed.

Protocol #28

Investigator 001 (Stephen Jones)

Twenty-four (24) patients, 8 male and 16 females were enrolled in the study. The frequency of the cancer types and therapies is given in Table 34.

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Table 34: Frequency of Cancer Types in the 001 Population

<u>Type</u> <u>Evaluable</u>	<u>Number</u>	<u>(%)</u>
Lymphoma	8	(33)
4		
Ovarian	4	(17)
1		
Breast	4	(17)
2		
Other	8	(33)
4		

The most common chemotherapy regimen was Adriamycin, Cytosan and vincristine, the usual therapy for lymphoma. The evaluability of patients by chemotherapy and sequence (cycle) is given in Table 35.

Table 35: Chemotherapy by Evaluability & Sequence Group
(Table 1, Sponsor's Analysis, Vol 1.11, Pg 339)

<u>Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>
Cisplatin & other combinations	2	1	3	3	0	3
Other combinations without cisplatin	<u>4</u>	<u>4</u>	<u>8</u>	<u>3</u>	<u>7</u>	<u>10</u>
Total	6	5	11	6	7	13

Eleven patients were terminated early. The reasons for early termination are listed in Table 36.

Table 36: Reasons for Early Termination
(Table 8, Sponsor's Analysis, Vol. 1.11, pg 349)

<u>Reason</u>	<u># of Patients</u>	<u>Patient #s</u>
Adverse experience (nabilone)	4	104, 109, 118, 126
Adverse experience (placebo)	2	113, 115
Lack of efficacy (placebo)	2	116, 121
Lack of efficacy (nabilone)	1	120
Chemotherapy changed	1	106
Adverse experience (unknown relationship to nabilone)	<u>1</u>	105
Total	11	

There were two other patients considered inevaluable due to protocol violations. Both patients skipped a dose of nabilone due to side effect severity. According to the study criteria, missed doses constituted a protocol violation. I am in agreement that these two patients should be considered inevaluable.

Sixteen (16) patients (67%) were receiving one or more concomitant medications. Four "completers" received prednisone during both courses of chemotherapy.

The sequence groups were comparable with respect to previous chemotherapy, sex, and age. However, a significant sequence by chemotherapy interaction was detected, the result of an imbalance of cisplatin chemotherapies in group 1 versus group 2.

The means of the efficacy variables are listed in Table 37. Nabilone appeared to reduce nausea and vomiting although there was overlap between the treatment groups when the standard deviation was taken into account. The investigator's global impression of efficacy favored nabilone. The relative and absolute differences in side effect ratings by investigators suggest that nabilone treatment was differentiable from placebo and produced a moderate level of interference with patient's functioning. The former point strongly infers that the double-blind nature of this study may have been compromised. Consequently, I would place greater weight on the most objective criterion; i.e., vomiting frequency. The investigator's impressions may have been biased by the recognition of the treatment being administered.

Table 37:
Descriptive Statistics of
Daily Averages and Investigator's Global Impressions
(Table 2, Sponsor's Analysis Vol 1.11, Appendix E, pg 449)

		Daily Averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	7.17	2.20	0.67	2.83	1.33
	S.D. n=6	4.92	0.69	0.82	1.72	1.21
Placebo	Mean	12.00	2.80	0.40	4.20	0.00
	S.D. n=5	3.67	0.45	0.55	0.84	0.00
Cycle 2						
Nabilone	Mean	10.20	2.40	0.40	3.00	2.00
	S.D. n=5	8.38	0.89	0.55	2.00	0.71
Placebo	Mean	15.17	2.97	0.37	3.83	0.33
	S.D. n=6	10.21	0.08	0.57	1.47	0.82
Both Cycles						
Nabilone	Mean	8.55	2.29	0.55	2.91	1.64
	S.D. n=11	6.53	0.76	0.69	1.76	1.03
Placebo	Mean	13.73	2.89	0.38	4.00	0.18
	S.D. n=11	7.76	0.30	0.53	1.18	0.60

The analysis of variance on the ranked data is shown in Table 38. There were no residual effects. There is a trend towards a period (cycle) effect on the vomiting frequency data. The results show that a significant effect on vomiting, favoring nabilone occurred ($p = .028$, one tailed). Even if a two-tailed test were used, the p value would be 0.056. This shows a striking difference when one considers that the data analysis utilized 11 patients who completed the study with no protocol violations. A similar effect is seen for severity of nausea, again favoring nabilone ($p = .034$, one-tailed or $.066$, two-tailed).

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Table 38:
 Non-Parametric Crossover Analysis on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.11, Appendix E, pg 173)

	Mean Ranks		z-value	P-value+
	Seq. Gp. 1 (n=6)	Seq. Gp. 2 (n=5)		
Residual Effects				
Freq. of Vomits - Average	6.17	5.80	-0.09	.500
- Day 1	6.17	5.80	-0.09	.500
Sev. of Nausea - Average	5.83	6.20	0.27	.500
- Day 1	5.92	6.10	0.18	.500
Food Intake - Average	6.33	5.60	-0.27	.500
- Day 1	6.33	5.60	-0.27	.500
Efficacy	5.58	6.50	0.55	.500
Adverse Effects	5.58	6.50	-0.55	.500
Treatment Effect				
Freq. of Vomits - Average	4.33	8.00	1.92	.028
- Day 1	4.33	8.00	1.92	.028
Sev. of Nausea - Average	4.42	7.90	1.83	.034
- Day 1	4.42	7.90	1.83	.034
Food Intake - Average	6.83	5.00	-0.82	.206
- Day 1	6.83	5.00	-0.82	.206
Efficacy	4.83	7.40	1.37	.085
Adverse Effects	8.08	3.50	-2.19	.014
Cycle Effect				
Freq. of Vomits - Average	4.75	7.50	-1.46	.144
- Day 1	4.75	7.50	-1.46	.144
Sev. of Nausea - Average	5.42	6.70	-0.73	.465
- Day 1	5.33	6.80	-0.82	.411
Food Intake Average	6.83	5.00	-0.82	.411
- Day 1	6.83	5.00	-0.82	.411
Efficacy	5.83	6.20	-0.27	.500
Adverse Effects	5.17	7.00	1.00	.315

+Residual and Period Effects are two-tailed.
 Treatment Effects are one-tailed.

Although the sponsor did not explain why a one-tailed analysis was chosen to examine treatment effects, I believe that since treatment superiority must be shown over placebo, the null hypothesis could be that a significant treatment effect exists favoring nabilone. Previous experience with nabilone in the "active control" studies would justify a one-tailed analysis.

The crossover frequency analysis of the categorical data (nabilone better, same, placebo better) failed to differentiate nabilone from placebo. The treatment effect for vomiting was $p = .262$. This is a likely results of the "collapsing" of the data down to 11 choices. The cycle 1 analysis of all patients also failed to differentiate treatment (efficacy) effects between nabilone and placebo. There was a significant increase in adverse effects in the nabilone group ($p = .009$, one-tailed). The failure to demonstrate treatment effects may be a result of the small numbers in the study groups. The nabilone vomiting frequency mean was less than half the placebo mean. The failure to demonstrate a treatment effect in cycle 1 patients may also be due to low vomiting frequency of three inevaluable (#104, 106 and 108) placebo patients. Had these three patients completed the crossover, the significant result attributed to nabilone may have been significantly diminished.

Investigator 002 (Lawrence Einhorn)

At the time of NDA submission, this study had not been completed. Forty-two (42) patients had enrolled in the study at that time. There were 23 male and 19 females, in- and outpatients, between the ages of 17 and 63. The cancer types are listed in Table 39.

Table 39: Frequency of Cancer Types in the Study Population

<u>Type</u>	<u>Frequency</u>	<u>(%)</u>	<u>Evaluable</u>
Testicular	19	(45)	15
Breast	14	(33)	12
Other	9	(22)	6

The most common chemotherapy regimen was cisplatin in combination with Adriamycin, vinblastine and bleomycin, the usual treatment for testicular cancer. The next most frequent treatment was a one-day administration of Adriamycin, 5-fluorouracil and cyclophosphamide, the usual treatment for patients with breast cancer.

The cancer chemotherapy by evaluability and sequence group is presented in Table 40 (Table 1, Sponsor's Analysis, Vol. 1.12, pg 15).

Table 40: Cancer Chemotherapy by Evaluability & Sequence Group

<u>Chemotherapy</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Gp. 1</u>	<u>Gp. 2</u>	<u>Total</u>	<u>Gp. 1</u>	<u>Gp. 2</u>	<u>Total</u>
Cisplatin + other combinations	7	11	18	2	1	3
Other combinations without cisplatin	<u>7</u>	<u>8</u>	<u>15</u>	<u>5</u>	<u>1</u>	<u>6</u>
Total	14	19	33	7	2	9

Thirty-three patients, 18 males and 15 females, were considered evaluable. Fourteen (42%) were in group 1 (nabilone on cycle 1) and 19 (58%) were in group 2 (placebo on cycle 1). Five patients (#220, 226, 234, and 240 - placebo cycle 2 and 237 - nabilone cycle 2) terminated "early" but were considered evaluable. The reasons for early study termination are listed in Table 41 (Table 8, Sponsor's Analysis, Vol. 1.12, pg 26).

Table 41: Reasons for Early Terminations

<u>Reason</u>	<u># Patients</u>	<u>Patient Numbers</u>
Drug-related (nabilone)	4	204, 205, 224, 237
Lack of efficacy (placebo)	4	220, 226, 234, 240
Lost to follow-up	1	211
Chemotherapy changed	1	243
Death due to cancer	<u>2</u>	213, 214
Total	12	

In addition to the early terminators, there were two patients (#222, 231) who completed the study but were ruled unevaluable due to differences in chemotherapy between the first and second cycles. I am in agreement that these two patients should have been excluded from the efficacy analysis. Further, I have evaluated the five early terminators that the sponsor deemed evaluable. I am in agreement that no protocol violations occurred and sufficient administration of both treatments was administered. Thus, I agree that 33/42 patients were evaluable.

One patient (#231) received prednisone on both chemotherapy cycles. I do not believe this could invalidate the study results.

There was a sequence group by evaluability interaction in the study; i.e., more patients were unevaluable in sequence group 1 than in sequence

group 2. The groups were comparable with respect to chemotherapy, previous chemotherapy, sex and age.

The results of the efficacy analysis are shown in Table 42. There is an apparent difference in the vomiting frequency and nausea severity scores across cycles for the placebo treatment. It is also interesting to note that the investigator rated nabilone more effective with a moderate effect on overall patient functioning.

Table 42:
Descriptive Statistics
Daily Averages and Investigator's Global Impressions
(Table 2, Sponsor's Analysis, Vol 1.12, Appendix E, pg 200)

		Daily averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	5.83	1.66	0.89	1.86	1.64
	S.D.	5.77	0.98	0.73	0.95	0.50
		n=14				
Placebo	Mean	8.05	1.85	0.80	3.32	0.11
	S.D.	9.17	0.91	0.57	1.34	0.32
		n=19				
Cycle 2						
Nabilone	Mean	2.93	0.85	0.81	1.74	1.63
	S.D.	4.25	0.57	0.56	0.87	0.68
		n=19				
Placebo	Mean	19.83	2.38	0.41	4.21	0.00
	S.D.	12.33	0.72	0.46	0.58	0.00
		n=14				
Both Cycles						
Nabilone	Mean	4.16	1.19	0.84	1.79	1.64
	S.D.	5.08	0.86	0.63	0.89	0.60
Placebo	Mean	13.05	2.08	0.63	3.70	0.06
	S.D.	12.00	0.87	0.56	1.16	0.24
		n=33				

The analysis of variance data are presented in Table 43. Significant residual effects were observed for day 1 and average vomiting frequency, day 1 and average nausea severity, and investigator rated efficacy. There was a treatment-related effect of nabilone to increase food intake. Investigator-rated adverse effects were significantly greater ($p < .001$) for nabilone.

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Table 43:
 Non-Parametric Crossover Analysis
 on Ranks
 (Table 4, Sponsor's Analysis, Vol 1.12, Appendix E, pg 202)

		Mean Ranks		Z-value	P-value+
		Seq. Gp. 1 (n=14)	Seq. Gp. 2 (n=19)		
Residual Effects					
Freq. of Vomits	- Average	22.89	12.66	3.02	.003
	- Day 1	23.00	12.58	3.08	.002
Sev. of Nausea	- Average	22.25	13.13	2.70	.007
	- Day 1	21.68	13.55	2.40	.016
Food Intake	- Average	15.32	18.24	-0.84	.402
	- Day 1	14.93	18.53	-1.04	.299
Efficacy		20.43	14.47	1.77	.077
Adverse Effects		16.32	17.50	-0.33	.500
Treatment Effect					
Freq. of Vomits	- Average	8.64	23.16		
	- Day 1	8.86	23.00		
Sev. of Nausea	- Average	10.14	22.05		
	- Day 1	9.86	22.26		
Food Intake	- Average	20.96	14.08	2.04	.021
	- Day 1	19.57	15.11	1.33	.092
Efficacy		7.96	23.66		
Adverse Effects		26.50	10.00	4.86	< .001
Cycle Effect					
Freq. of Vomits	- Average	12.39	20.39		
	- Day 1	12.14	20.58		
Sev. of Nausea	- Average	19.11	15.45		
	- Day 1	19.64	15.05		
Food Intake	Average	20.18	14.66	1.64	.101
	- Day 1	20.04	14.76	1.57	.117
Efficacy		14.25	19.03		
Adverse Effects		17.96	16.29	0.51	.500

+Residual and Period Effects are two-tailed.
 Treatment Effects are one-tailed.

Results of the categorical analysis are shown in Table 44. Highly significant results favoring nabilone were demonstrated on the following parameters: day 1 ($p < .001$) and average vomiting frequency ($p < .001$), severity of nausea, day 1 ($p < .001$) and average ($p < .005$), investigator-rated efficacy ($p < .001$) and patient preference ($p < .001$). I asked Dr. Nevius for a consultation on this aspect of the Sinhorn study. He agreed that the sponsor had followed the appropriate statistical dictum of not calculating treatment effects when a residual effect had been demonstrated. He recalculated the data, ignoring the residual effect. Highly significant results favoring nabilone were obtained. Thus, "ignoring the residual", one would obtain close agreement between the analysis of variance and the categorical analysis.

(Table 44
Crossover Frequency Analysis
(Tables 6A & 6B) Sponsor's Analysis, Vol 1.12, Appendix E, pg 205)

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u> <u>Gp. 1</u>	<u>Seq.</u> <u>Gp. 2</u>	<u>Total</u>	<u>Cycle</u> <u>Effect+</u>	<u>Treatment</u> <u>Effect++</u>
Freq. of vomits - Average					
Nabilone better	13	16	29	.5	<.001
Same	0	0	0		
Placebo better	1	3	4		
Freq. of vomits - Day 1					
Nabilone better	13	16	29	.5	<.001
Same	0	0	0		
Placebo better	1	3	4		
Severity of Nausea - Average					
Nabilone better	7	14	21	.5	<.005
Same	5	2	7		
Placebo better	2	3	5		
Severity of Nausea - Day 1					
Nabilone better	6	15	21	.5	<.001
Same	7	2	9		
Placebo better	1	2	3		
Food Intake - Average					
Nabilone better	7	6	13	.450	.057
Same	6	9	15		
Placebo better	1	4	5		
Food Intake - Day 1					
Nabilone Better	6	3	9	.265	.280
Same	7	12	19		
Placebo better	1	4	5		
Clinical Global Impressions					
Efficacy					
Nabilone better	13	14	27	.5	<.001
Same	1	4	5		
Placebo better	0	1	1		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	0	0	0	.5	<.001
Same	0	1	1		
Placebo better	14	18	32		
Patient's preference					
Nabilone better	14	16	30	.5	<.001
Same	0	2	2		
Placebo better	0	1	1		

+Two-Tailed, ++One-Tailed

The sponsor also performed a cycle 1 all-patients analysis (Table 45). Although there were no patient-rated variables which attained statistical significance, the investigator rated nabilone more efficacious (p = .004) and moderately affecting patient's ability to function.

Table 45 (Table 8, Sponsor's Analysis, Vol 1.12, Appendix E, pg 208)
Cycle 1 - All Patients

	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
	Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone								
(n=19) Mean	5.78	8.53	1.42	1.74	0.92	0.84	2.11	1.68
S.D.	5.98	7.86	0.86	1.10	0.70	0.76	1.05	0.48
Median	4.40	7.00	1.80	2.00	1.00	1.00	2.00	2.00
Placebo								
(n=19) Mean	8.02	9.68	1.83	2.21	0.79	0.79	3.32	0.11
S.D.	9.19	8.79	0.92	0.85	0.58	0.63	1.34	0.32
Median	2.60	7.00	2.00	2.00	1.00	1.00	4.00	0.00

Non-Parametric Analysis

Mean Rank								
Nabilone	18.89	18.95	17.37	17.21	20.66	19.74	14.71	23.68
Placebo	20.11	20.05	21.63	21.79	18.34	19.26	24.29	10.32
Z-value	0.35	0.32	1.20	1.28	-0.63	-0.12	2.67	-5.08
P-value	.363	.374	.116	.099	.265	.453	.004	.001

*One-tailed

Investigator 003 (Frank Greco)

Fourteen (14) patients, 4 males and 10 females, were enrolled in this study. Patients were between the ages of 37 and 67 years old. The major tumor types were ovarian cancer (4/14), breast cancer (4/14), lung cancer (2/14) and other cancers (4/14). The most frequent chemotherapy regimen consisted of a one-day treatment of Adriamycin, Cytosan, hexamethylmelamine and cisplatin, given to 4 patients with ovarian cancer.

Five (5) patients, 1 male and 4 females, were considered evaluable for efficacy. There were 5 early terminations, 1 protocol deviation and 3 patients whose chemotherapy was changed in cycle 2.

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Eight (8) patients received one or more concomitant medications. None of the five evaluable patients received prednisone or dexamethasone.

The small sample size precluded a statistical analysis. Of the evaluable patients, nabilone produced less vomiting, less nausea, a better investigator efficacy rating and higher incidence of side effects. Four of the five patients preferred nabilone.

Investigator 004 (John Durant)

Sixteen (16) patients, 7 male and 9 female were enrolled in the study. Patients were between the ages of 16 and 80. Five (5) patients (31%) had breast cancer, 4 (25%) had lung cancer and 2 (13%) had lymphoma. The remaining five patients each had a different type of cancer.

The usual chemotherapy regimen was a one-day multiple drug administration. The most frequent combinations were Cytosan, Adriamycin, and one other additional agent (vincristine, 5-fluorouracil, cisplatin, methotrexate, etc.).

Eight (8) patients 4 male and 4 female were considered evaluable for the efficacy analysis. Four patients (#405, 412, 415 and 416) dropped out before completing the crossover due to adverse effects associated with nabilone. One (#401) patient dropped out due to lack of placebo efficacy. Patient #406 was dropped due to progressive disease. Patient #414 had her chemotherapy changed, making her unevaluable. Patient #418 was terminated before completion due to a flare-up of chronic rheumatoid arthritis.

Patient #402 received prednisone on both cycles of chemotherapy. I do not believe this compromises the results obtained in this patient. There was no difference in efficacy between nabilone and placebo in this patient.

The results obtained with the eight patients were not subjected to statistical analysis. However, visual inspection of the data supports nabilone superiority with respect to all patient and investigator-related efficacy variables. The investigators also rated nabilone as producing more side effects than placebo, which produced none. In spite of the greater side effect severity, 6/8 patients preferred nabilone.

The results of investigators 003 and 004 are tabulated and analyzed in the composite analysis.

I have one further comment that reinforces a previous remark about the compromise of the double-blind. It appears in both studies 003 and 004 that the blinding of the study was compromised by the ease of differentiability of the treatments, based on the nature and frequency of the side effects.

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Investigator 005 (Martin Levitt)

This study was still in progress at the time of the NDA submission. The sponsor reported data on 58 patients, 25 male and 33 female, who enrolled in the study. Patient ages ranged from 17 to 79. Thirty-six (36) patients, 12 males and 24 females, with an average age of 53.6 years were considered evaluable for the study. The frequency of cancer type is listed in Table 46.

Table 46: Frequency of Cancer Type & Evaluability in Patient Population

<u>Type</u>	<u>Frequency</u>	<u>(%)</u>	<u>Evaluable</u>
Lung	21	(36)	10
Ovarian	11	(19)	9
Breast	10	(17)	10
Other	16	(28)	7

Cancers in the "other" category occurred with a frequency of 3 or less.

The sequence groups were comparable with respect to chemotherapy. The most common treatment was a combination of Adriamycin, cyclophosphamide, VP-16, vincristine or cisplatin. The cancer chemotherapy regimen by evaluability tabulation is listed in Table 47. (Table 1, Sponsor's Analysis, Vol. 1.13, pg 16).

Table 47: Cancer Chemotherapy by Evaluability & Sequence Group

<u>Chemotherapy Regimen</u>	<u>Evaluable</u>			<u>Unevaluable</u>		
	<u>Group 1</u>	<u>Group 1</u>	<u>Total</u>	<u>Group 1</u>	<u>Group 2</u>	<u>Total</u>
Cisplatin and other combinations	4	8	12	7	4	11
Other combinations without cisplatin	<u>11</u>	<u>13</u>	<u>24</u>	<u>6</u>	<u>5</u>	<u>11</u>
Totals	15	21	36	13	9	22

Twenty (20) patients terminated the study before completing the crossover. The reasons for termination are given in Table 48 (Table 8, Sponsor's Analysis, Vol. 1.13, pg 26).

Table 48: Reasons for Early Terminations

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse effect (nabilone)	5	504, 516, 517, 566, 578
Adverse effect - no drug relationship)	1	577
Lack of efficacy (placebo)	1	508
Lack of efficacy (nabilone)	1	563
Patient decision	2	570, 575
Complicating decisions	1	1
Lost to follow-up	4	526, 533, 568, 574
Chemotherapy changed	4	519, 521, 541, 567
Death due to cancer	2	512, 564

Patient #504 actually was evaluable for 1 day of the crossover. Additionally, three patients (#507, 532, 536) who completed the crossover were judged unevaluable. I am in agreement that these three patients each had a protocol violation. Further, I agree that 36 patients were evaluable.

In this study, only one day of cancer chemotherapy was given. Forty-two patients received 4 mg of nabilone while 5 patients received only a 2 mg dose on the day of chemotherapy. All nabilone patients also received 2 mg on the evening prior to chemotherapy.

Sixteen (16) patients received one or more concomitant medications. One patient (#540) received prednisone during both cycles of the crossover. This patient was receiving prednisone as an adjunct to her chemotherapy for breast cancer. Serum chemistry analyses were not available for this patient. At any rate, one of 36 patients receiving prednisone is unlikely to bias the study.

Analysis of sequence group comparability revealed that the groups were comparable with respect to chemotherapy, previous chemotherapy, sex, and age.

The patient and investigator-rated descriptive variables are tabulated in Table 49 (Table 1, Sponsor's Analysis, Vol. 1.13, Appendix E, pg 177). The data suggest a potent antiemetic effect of nabilone. The side effect difference in the last column also suggests that the study blind was compromised.

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Table 49
Descriptive Statistics
Efficacy and Safety Parameters

		<u>Freq. of Vomits</u>	<u>Severity of Nausea</u>	<u>Food Intake</u>	<u>Investigator's Global Impressions</u>	
					<u>Efficacy</u>	<u>Adverse Effects</u>
Cycle 1						
Nabilone	Mean	1.71a	0.87	1.67	1.93	1.07
	S.D.	3.95	1.23	1.29	1.33	0.80
n=15						
Placebo	Mean	7.33b	2.19	0.62	3.81	0.00
	S.D.	6.42	0.68	0.97	1.08	0.00
n=21						
Cycle 2						
Nabilone	Mean	3.94a	1.14	1.00	2.33	1.52
	S.D.	5.62	1.11	1.18	1.43	0.60
n=21						
Placebo	Mean	7.64b	2.33	0.33	3.60	0.07
	S.D.	5.75	0.82	0.49	0.83	0.26
n=15						
Both Cycles						
Nabilone	Mean	2.97c	1.03	1.28	2.17	1.33
	S.D.	5.01	1.11	1.26	1.38	0.72
n=36						
Placebo	Mean	7.47c	2.25	0.50	3.72	0.03
	S.D.	6.04	0.73	0.71	0.97	0.17
n=36						

a n=14, b n=18, c n=32

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Table 50:
 Non-Parametric Crossover Analysis on Ranks
 (Table 3, Sponsor's Analysis, Vol 1.13, Appendix E, pg 179)

	Mean Ranks		Z-value	P-value+
	Seq. Gp. 1 (n=15)	Seq. Gp. 2 (n=21)		
Residual Effects				
Freq. of Vomits	17.97	18.88	-0.24	.500
Sev. of Nausea	17.93	18.90	-0.26	.500
Food Intake	20.10	17.36	0.79	.432
Efficacy	16.63	19.83	-0.88	.378
Adverse Effects	15.73	20.48	-1.32	.188
Treatment Effect				
Freq. of Vomits	9.20	25.14	-4.46	<.001
Sev. of Nausea	9.27	25.10	-4.43	<.001
Food Intake	24.67	14.10	2.98	<.001
Efficacy	9.37	25.02	-4.38	<.001
Adverse Effects	28.63	11.26	4.89	<.001
Period Effect				
Freq. of Vomits	17.50	19.21	-0.47	.500
Sev. of Nausea	16.43	19.98	-0.98	.328
Food Intake	21.97	16.02	1.68	.092
Efficacy	17.37	19.31	-0.53	.500
Adverse Effects	15.37	20.74	-1.49	.136

+Residual and Period Effects are two-tailed.
 Treatment Effects are one-tailed.

The analysis of variance of the ranked data is presented in Table 50. There were no residual effects observed on any of the five parameters. There was also no difference noted with respect to period effects on the parameters. A large treatment effect favoring nabilone occurred on every patient and investigator-rated efficacy variable ($p = .001$ or less). However, a significant difference in adverse effects was noted between nabilone and placebo ($p < .001$).

The results of the categorical analysis are listed in Table 51. Nabilone was rated superior to placebo on patient and investigator-rated efficacy variables. Further analysis showed nabilone to be equieffective against cisplatin versus non-cisplatin regimens (data not shown). Moreover, patients preferred nabilone to placebo ($p < .001$). This is of importance as nabilone was associated with a greater incidence and severity of side effects.

Table 51
Crossover Frequency Analysis

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u>	<u>Seq.</u>	<u>Total</u>	<u>Cycle</u>	<u>Treatment</u>
	<u>Gp. 1</u>	<u>Gp. 2</u>			
Freq. of vomits					
Nabilone better	13	16	29	.5	.001
Same	0	3	3		
Placebo better	2	2	4		
Severity of Nausea					
Nabilone better	11	15	26	.5	.001
Same	4	4	8		
Placebo better	0	2	2		
Food Intake					
Nabilone better	10	9	19	.430	.004
Same	4	8	12		
Placebo better	1	4	5		
Clinical Global Impressions					
Efficacy					
Nabilone better	11	17	28	.5	.001
Same	3	2	5		
Placebo better	1	2	3		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	1	0	1	.5	.001
Same	3	0	3		
Placebo better	11	21	32		
Patient's preference					
Nabilone better	12	16	28	.5	.001
Same	2	3	5		
Placebo better	1	2	3		

+Two-Tailed, ++One-Tailed

The "all patients" cycle 1 analysis is presented in Table 52. Statistically significant results ($p = .01$ or less) favoring nabilone were observed for the patient-rated variables. Investigator-rated efficacy was also statistically significant, favoring nabilone ($p .001$). Adverse effects were rated as higher for nabilone ($p .001$) by the investigator. The adverse effect data were actually lower than comparable data in evaluable patients. (See Table 49)

Table 52:
Descriptive Statistics and Test Results
Cycle 1 - All Patients
 (Table 7, Sponsor's Analysis, Vol 1.13, Appendix E, pg 185)

		Freq. of Vomits	Severity of Nausea	Food Intake	Investigator's Global Impressions	
					Efficacy	Adverse Effects
Nabilone	Mean	3.74	0.83	1.30	2.05a	1.14a
	S.D.	7.54	1.07	1.18	1.36	0.89
	Median	1.00	0.00	1.00	1.00a	1.00a
Placebo	Mean	7.65b	2.26	0.56	3.93	0.04
	S.D.	6.03	0.71	0.89	1.07	0.19
	Median	7.00	2.00	0.00	4.00	0.00

Non-Parametric Analysis

Mean Rank	Nabilone	17.61*	16.20	30.63	15.70	34.50
	Placebo	32.22*	33.43	21.13	32.57	17.26
Z-value		-3.52	-4.16	2.31	-4.10	4.21
P-value		.001	.001	.011	.001	.001

+One-tailed

*n=22, b_n=23

Comments:

This study demonstrates a superior antiemetic effect of nabilone over placebo. Arguments regarding possible bias introduction due to dropouts are weakened by the highly significant effects favoring nabilone in the "all patients" cycle 1 analysis. Thus, this study provides persuasive evidence of an antiemetic effect without the possible bias incurred by dropping out "unevaluable" patients.

The patient population in this study was heterogeneous from a diagnostic standpoint. Consequently, no cancer type or chemotherapy regimen can be singled out as being highly susceptible to nabilone treatment. Further, I would doubt that an agency-conducted post-hoc analysis could determine a significant antiemetic effect in any of the cancer subgroups. This is, in part, due to the low numbers of patients in the subgroups (7 to 12). Thus, I would not recommend highlighting nabilone efficacy against, for example, cancer chemotherapy regimens for breast cancer.

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The side effect profile of nabilone probably unmasked the double-blind in this study. Although this could lead to expectation effects, vomiting frequency is, for the most part, an objective parameter not without some psychological component. However, I believe the drug effect overshadows any benefit gained from an expectation of efficacy. Nausea and food intake ratings are more subjective, and would be more subject to bias. However, the potency of the effect argues that a drug component far overshadows any psychological component.

Investigator 006 (John Gunne.)

This study was still in progress at the time of the NDA submission. Forty-five (45) patients, 20 males and 25 females, were enrolled in the study. Thirty-six patients, 16 males and 20 females with an average age of 56.2 years, were considered evaluable for efficacy. The frequency of cancer types is listed in Table 53.

Table 53: Frequency of Cancer Type & Evaluability in Patient Population

Type	Frequency	(%)	Evaluable
Breast	14	(31)	11
Lung	10	(22)	8
Ovarian	4	(9)	3
Other	17	(38)	14

Cancers in the "other" category occurred with a frequency of 3 or less.

The sequence groups were comparable with respect to chemotherapy. The most common treatments administered were Adriamycin, 5-Fluorouracil, cyclophosphamide, and methotrexate. These agents were used in various combinations to treat lung and breast cancer. The cancer chemotherapy by evaluability is listed in Table 54 (Table 1, Sponsor's Analysis, Vol. 1.13, pg 214).

Table 54: Cancer Chemotherapy by Evaluability & Sequence Group

Chemotherapy Regimen	Evaluable			Unevaluable		
	Group 1	Group 2	Total	Group 1	Group 2	Total
Cisplatin and other combinations	6	2	8	0	2	2
Combinations without cisplatin	13	15	28	4	3	7
Totals	19	17	36	4	5	9

Ten (10) patients were terminated early. The reasons for early termination are given in Table 55 (Table 7), Sponsor's Analysis, Vol. 1.13, pg 223).

Table 55: Reasons for Early Terminations

<u>Reason</u>	<u>#Patients</u>	<u>Patient Numbers</u>
Adverse effect (nabilone)	4	609, 625, 639, 704
Lack of efficacy (placebo)	3	603, 647, 649
Patient decision	2	619, 713
Death due to cancer	<u>1</u>	621
Total	10	

Patient #603 discontinued after his third placebo dose during the second cycle. Patient #625 was considered unevaluable due to a protocol violation. Thus, 36 patients were considered evaluable.

Chemotherapy regimens usually lasted only 1 day. Only 2 evaluable patients received more than 1 day of chemotherapy. However, data are displayed as both day 1 and "average" effects. All nabilone patients received a 2 mg dose on the evening preceding chemotherapy initiation and 40/41 received 4 mg of nabilone on day 1 of chemotherapy.

Thirty-nine (39) patients were receiving concomitant medications. Analgesics were the most common study drug administered. Two patients receive prednisone during both chemotherapy cycles. I do not believe these 2 patients could bias the results (in case there is an antiemetic effect of prednisone).

The sequence group comparisons noted that the groups were comparable with respect to chemotherapy, prior chemotherapy, sex and age.

The patient and investigator-rated variables are tabulated in Table 56 (Table 2, Sponsor's Analysis, Vol. 1.13, pg 364). Nabilone appears to exert a moderate antiemetic effect. The anti-nauseant effect of nabilone appears more potent, relative to the antiemetic effect. The investigator's impression of efficacy suggest nabilone is more efficacious; the average nabilone response equaled a good rating.

Table 56:
Descriptive Statistics
Daily Averages and Investigator's Global Impressions

		Daily averages			Investigator's Global Impressions	
		Freq. of Vomits	Severity of Nausea	Food Intake	Efficacy	Adverse Effects
Cycle 1						
Nabilone	Mean	5.53	1.21	1.37	2.26	0.89
	S.D. n=19	7.97	1.13	0.83	1.15	0.57
Placebo	Mean	6.59	2.00	0.88	3.47	0.06
	S.D. n=17	10.39	1.06	0.78	1.18	0.24
Cycle 2						
Nabilone	Mean	3.41	1.29	1.29	2.00	1.12
	S.D. n=17	5.80	1.10	0.92	0.87	0.70
Placebo	Mean	7.12	2.11	0.95	3.58	0.05
	S.D. n=19	8.15	0.81	0.71	1.35	0.23
Both Cycles						
Nabilone	Mean	4.53	1.25	1.33	2.14	1.00
	S.D.	7.02	1.11	0.86	1.02	0.63
Placebo	Mean	6.87	2.06	0.92	3.53	0.06
	S.D. n=36	9.14	0.92	0.73	1.25	0.23

The analysis of variance data are presented in Table 57. There were no residual or period effects which reached statistical significance. There were patient-rated and investigator-rated efficacy variables which attained statistical significance, favoring nabilone. The following effects favored nabilone: day 1 ($p = .009$) and average vomiting frequency ($p = .003$), day 1 nausea severity ($p < .001$) and average severity of nausea ($p < .001$), day 1 food intake ($p = .016$) and average daily food intake ($p = .016$), and investigator-rated global efficacy ($p < .001$). Adverse effect incidence was more severe in the nabilone group ($p < .001$).

When the effects of nabilone on nausea and vomiting are compared, nabilone appears to exert a greater anti-nauseant effect relative to the antiemetic effect.

Table 57:
Non-Parametric Crossover Analysis on Ranks
(Table 4, Sponsor's Analysis, Vol 1.13, Appendix E, pg 366)

		Mean Ranks		Z-value	P-value+
		Seq. Gp. 1 (n=19)	Seq. Gp. 2 (n=17)		
Residual Effects					
Freq. of Vomits	- Average	19.21	17.71	-0.41	.500
	- Day 1	19.08	17.85	-0.33	.500
Sev. of Nausea	- Average	18.68	18.29	-0.10	.500
	- Day 1	18.68	18.29	-0.10	.500
Food Intake	- Average	18.66	18.32	-0.08	.500
	- Day 1	18.66	18.32	-0.08	.500
Efficacy		19.61	17.26	-0.65	.500
Adverse Effects		16.84	20.35	1.01	.311
Treatment Effect					
Freq. of Vomits	- Average	14.53	22.94	2.41	.008
	- Day 1	14.61	22.85	2.36	.009
Sev. of Nausea	- Average	13.16	24.47	3.23	<.001
	- Day 1	13.16	24.47	3.23	<.001
Food Intake	- Average	22.08	14.50	-2.14	.016
	- Day 1	22.08	14.50	-2.14	.016
Efficacy		12.29	25.44	3.76	<.001
Adverse Effects		25.95	10.18	-4.47	<.001
Period Effect					
Freq. of Vomits	- Average	19.34	17.56	-0.49	.500
	- Day 1	19.39	17.50	-0.52	.500
Sev. of Nausea	- Average	18.00	19.06	0.32	.500
	- Day 1	18.00	19.06	0.32	.500
Food Intake	Average	18.58	18.41	-0.03	.500
	- Day 1	18.58	18.41	-0.03	.500
Efficacy		18.76	18.21	-0.14	.500
Adverse Effects		17.00	20.18	0.92	.358

+Residual and Period Effects are two-tailed.
Treatment Effects are one-tailed.

The results of the categorical analysis are presented in Table 58 (Tables 6A&B, Sponsor's Analysis, Vol. 1.13, Appendix E, Pg 368-9). There was a trend ($p = .103$) favoring nabilone on the vomiting data. Highly significant effects favoring nabilone were noted for day 1 ($p < .001$) and average nausea severity ($p < .001$). Food intake also showed statistically significant effects, favoring nabilone ($p = .032$ for day 1 and average daily intake). Patients also preferred nabilone 25 to 9 ($p = .007$); a higher incidence of adverse events was recorded in the nabilone group.

Table 58
Crossover Frequency Analysis

	<u>Frequency of Patients</u>			<u>P-Value</u>	
	<u>Seq.</u>	<u>Seq.</u>	<u>Total</u>	<u>Cycle</u>	<u>Treatment</u>
	<u>Gp. 1</u>	<u>Gp. 2</u>			
Freq. of vomits - Average					
Nabilone better	10	10	20	.500	.103
Same	3	2	5		
Placebo better	6	5	11		
Freq. of vomits - Day 1					
Nabilone better	10	10	20	.500	.103
Same	3	2	5		
Placebo better	6	5	11		
Severity of Nausea - Average					
Nabilone better	12	11	23	.500	<.001
Same	5	4	9		
Placebo better	2	2	4		
Severity of Nausea - Day 1					
Nabilone better	12	11	23	.500	<.001
Same	5	4	9		
Placebo better	2	2	4		
Food Intake - Average					
Nabilone better	6	6	12	.500	.032
Same	12	9	21		
Placebo better	1	2	3		
Food Intake - Day 1					
Nabilone Better	6	6	12	.500	.032
Same	12	9	21		
Placebo better	1	2	3		
Clinical Global Impressions					
Efficacy					
Nabilone better	13	12	25	.500	<.001
Same	3	2	5		
Placebo better	3	3	6		
Clinical Global Impressions					
Adverse Effects					
Nabilone better	1	1	2	.500	<.001
Same	3	2	5		
Placebo better	15	14	29		
Patient's preference					
Nabilone better	13	12	25	.500	.007
Same	2	0	2		
Placebo better	4	5	9		

+Two-Tailed, ++One-Tailed

The results of the "all patients" cycle 1 analysis are shown in Table 59 (Table 8, Sponsor's Analysis, Vol. 1.13, Appendix E, pg 372). A trend favoring nabilone on day 1 vomiting frequency is evident (p = .083). In fact, the same data with 3 or 4 more patients/group would attain significance at the p = .05 level. As this study was in progress at the time of the NDA submission, the results of the first period may attain significance when an update of the completed study is submitted.

Nabilone's effect attained statistical significance on day 1 (p = .006) and average nausea severity (p = .017), day 1 food intake (p = .024) and average food intake (p = .047) and investigator-rated global efficacy (p = .005). The results suggest that the investigator may have keyed on nausea and food intake rather than vomiting frequency in assessing efficacy.

Table 59:
Cycle 1 - All Patients Analysis
(Table 8, Sponsor's Analysis, Vol 1.12, Appendix E, pg 208)

	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
	Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone								
(n=21) Mean	5.48	5.48	1.26	1.26	1.35	1.35	2.48	1.13
S.D.	7.64	7.64	1.10	1.10	0.78	0.78	1.16	0.81
Median	1.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00
Placebo								
(n=21) Mean	9.13*	10.85*	2.00	2.19	0.89	0.81	3.52	0.05
S.D.	15.70	16.07	1.06	1.03	0.81	0.75	1.29	0.22
Median	4.00	4.00	2.00	3.00	1.00	1.00	4.00	0.00
Non-Parametric Analysis								
Mean Rank								
Nabilone	20.52	19.96	18.61	17.61	25.63	26.20	17.72	30.78
Placebo	24.67	25.29	26.76	27.86	19.07	18.45	27.74	13.43
Z-value	1.08	1.39	2.11	2.66	-1.68	-1.99	2.60	-4.46
P-value+	.140	.083	.017	.006	.047	.024	.005	<.001
+One-tailed								
*n=20								

Comments:

The results of this study demonstrate a salutary effect of nabilone over placebo on nausea and vomiting associated with cancer chemotherapy. The effect on nausea was more notable than the effect on vomiting. However, the analysis of variance of the ran data found statistically significant effects favoring nabilone on the emesis variables.

As in the other studies reviewed, the side effect profile probably unmasked the study blind. Thus, more credence should be given to the vomiting frequency data and less to the patient-rated nausea variables. Consequently, the results of the study are somewhat diminished in importance as a greater anti-nauseant effect was observed. However, the analysis of variance demonstrated a significant ($p = .008$) effect of nabilone on vomiting frequency. In the cycle 1 all patients analysis, a nearly-significant ($p = .085$) result was obtained. The results of the study may be more positive for nabilone when all the data are submitted.

Composite analysis - Protocol 28

The sponsor analyzed the data from the six centers which comprised the study. Of the 199 patients that were entered, 129 patients were evaluable. A significant sequence group by evaluability effect occurred, i.e., more patients were unevaluable in sequence group 1 than in group 2.

Analysis of the groups with respect to treatment parameters and patient demographics revealed several statistically significant investigator interactions. A significant investigator by evaluability effect was noted ($p < .001$); the proportion of evaluable patients varied significantly across investigators. Investigator interactions were also noted for chemotherapy ($p = .036$), prior chemotherapy ($p = .012$), evaluability by prior chemotherapy ($p = .014$), and age ($p < .001$).

Comment:

In terms of clinical ramifications, this strongly suggests that only general conclusions could be made in the composite analysis. The treatment variables exhibit significant heterogeneity, making conclusions about treatment versus cancer type chemotherapy or treatment efficacy in the face of previous chemotherapy a hazardous undertaking. Consequently, the composite results can only be discussed in a general way; i.e., whether nabilone was superior to placebo treatment in the treatment of nausea and emesis associated with (a variety of) cancer chemotherapy regimens. Given the caveat that a composite analysis of this study could only be used to support a general labeling claim, I have no objections to the results being combined and analyzed.

The cancer type by evaluability is listed in Table 60 (Table 1, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 312). The rank order of evaluable cancer types was: breast > lung > testis > ovary > lymphoma > Hodgkins. All other evaluable cancers occurred with a frequency of 3 or less.

Comment:

The patient population differs from those in the two active control trials in which nabilone demonstrated efficacy. Patients with testicular cancer were the predominant patient group in those studies.

Table 60
Comparison of Sequence Groups and
Evaluability Groups for Type of Cancer

Chemotherapy Regimen	Evaluable			Unevaluable		
	Seq. Group 1	Seq. Group 2	Total	Seq. Group 1	Seq. Group 2	Total
Adenocarcinoma	1	0	1			
Bladder	0	2	2	0	1	2
Bone				2	0	2
Breast	17	20	37	9	6	15
Cervix				1	0	1
Colon	1	1	2	1	0	1
Connective Tissue	0	3	3			
Esophagus				1	0	1
Fallopian Tube	0	1	1	1	0	1
Germinoma	0	1	1			
Hodgkin's	3	2	5	1	1	2
Kidney	0	1	1			
Larynx	1	0	1	1	1	2
Leukemia				1	0	1
Lung	8	15	23	8	7	15
Lymphoma	4	4	8	5	2	7
Lymphoma Non-Hod-kin's				0	1	1
Melanoma	1	1	2	0	2	2
Mesothelioma	0	1	1			
Ovary	7	8	15	5	3	8
Pancreas	1	0	1			
Parotoid Gland				0	1	1
Pharynx				1	0	1
Prostate	1	2	3			
Rectum	1	0	1			
Squamous Cell				0	1	1
Stomach	1	0	1			
Testis	8	10	18	4	1	5
Thyroid	1	0	1			
Uterus	1	0	1	0	1	1
Unknown				0	1	1
Total	57	72	129	41	29	70

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Forty-five of the 129 evaluable patients received cisplatin-based regimens. However, investigator #002 had a residual effect for vomiting in his study which caused 18 cisplatin patients and 15 non-cisplatin (33 total) patients to be dropped from the analysis. Therefore, only 27 of 96 evaluable patients received cisplatin in the analysis of certain efficacy variables (vide infra). This explains why results will be expressed as both with an "n" of 129 and an "n" of 96. The chemotherapy distribution also suggests that nabilone would need to be effective in noncisplatin-based regimens. This takes on more importance than usual because nabilone has already proved efficacious against cisplatin in active controlled trials (vide supra).

The results of the patient and investigator-rated results are tabulated in Table 61 as a function of investigator. In each case, the nabilone treatment means favor a superior antiemetic and antinauseant effect of nabilone. The investigators all rated nabilone as being both efficacious and producing a higher incidence of adverse events.

Table 61:
Means

Both Cycles Combined
(Table 3C, Sponsor's Analysis, Vol 1.11, Appendix K, pg 319)

Drug	Investigator	n	Freq. of Vomits		Severity of Nausea		Food Intake		Investigator's Global Impressions	
			Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects
Nabilone	001	11	2.55	8.55	2.29	2.27	0.55	0.55	2.91	1.64
	002	33	4.16	5.58	1.19	1.45	0.84	0.75	1.79	1.64
	003	5	10.27	15.20	1.73	2.00	1.20	1.20	2.20	1.00
	004	8	2.33 ^a	2.33 ^a	1.75	1.75	1.00	1.00	1.63	1.38
	005	36	2.97 ^b	2.97 ^b	1.03	1.03	1.28	1.28	2.17	1.33
	006	36	4.53	4.53	1.25	1.25	1.33	1.33	2.14	1.00
Composite		129	4.51 ^c	5.09 ^c	1.31	1.39	1.10	1.09	2.09	1.33
		(96)	(4.64) ^d	(4.91) ^d						
Placebo	001	11	13.73	13.73	2.83	2.91	0.38	0.36	4.00	0.18
	002	33	13.05	15.03	2.08	2.39	0.63	0.61	3.70	0.06
	003	5	34.60	36.80	2.67	2.80	0.40	0.40	3.40	0.20
	004	8	14.83 ^a	14.83 ^a	2.75	2.75	0.63	0.63	4.38	0.00
	005	36	7.47 ^b	7.47 ^b	2.25	2.25	0.50	0.50	3.72	0.03
	006	36	6.87	6.86	2.06	2.06	0.92	0.92	3.53	0.06
Composite		129	10.81 ^c	11.43 ^c	2.25	2.34	0.64	0.64	3.71	0.06
		(96)	(9.99 ^d)	(10.11 ^d)						

a_n=6, b_n=32, c_n=123, d_n=90
() = without investigator 002

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The composite analysis of variance is presented in Table 62 (Table 5, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 323). There is a significant investigator effect in the analysis of residuals for all patient-rated variables and an investigator by residual interaction for day 1 and average vomiting frequency. When the sponsor removed investigator #002 from the analysis, the interaction disappeared. Thus, the treatment effect for vomiting frequency was calculated after omitting the data from investigator #002. There was a significant investigator effect, suggesting a differential response on day 1 vomiting across investigators. There were investigator x treatment interactions for day 1 ($p = .019$) and average vomiting frequency ($p = .01$), and adverse effects ($p = .042$). The treatment effects were calculated by dividing the treatment SS by the investigator x treatment SS. Treatment effects favoring nabilone at the $p = .02$ level or less were noted on all patient- and investigator-rated efficacy variables. Nabilone also produced a greater incidence of adverse effects ($p < .001$).

Table 62
Crossover Analysis of Variance on Ranks

Residual Effect	Investigator		Residual		Inv. x Residual		Error S.S.C
	S.S.a	P	S.S.b	P	S.S.a	P	
Freq. of Vomits - Average	21997	.003	112	.500	13070	.054	136118
- Day 1	30688	.001	2	.500	12929	.047	130455
Sev. of Nausea - Average	22284	.003	404	.500	9229	.170	136717
- Day 1	27244	.001	298	.500	9124	.168	134611
Food Intake - Average	14935	.052	1181	.346	2512	.500	154316
- Day 1	15944	.036	961	.390	3395	.500	151018
Efficacy	5292	.500	1245	.336	9328	.228	155643
Adverse Effects	21934	.001	216	.500	9445	.095	115173
Removing INV = 002							
Freq. of Vomits - Average	11467 ^d	.006	563	.360	1781 ^d	.500	57256 ^e
- Day 1	11608 ^d	.003	299	.500	1804 ^d	.500	56603 ^d
Treatment Effect							
Freq. of Vomits+ Average	1384 ^d	.476	19969	.010*	5525 ^d	.016	
3355 ^e							
- Day 1	5473 ^d	.011	10647	.021*	4880 ^b	.019	33729 ^e
Sev. of Nausea - Average	1603	.500	29998	<.001	3036	.500	94793
- Day 1	2812	.500	26593	<.001	3001	.500	91510
Food Intake - Average	4350	.500	12463	<.001	3799	.500	118295
- Day 1	4534	.478	11234	<.001	4716	.454	116427
Efficacy	3484	.407	32274	<.001	4510	.258	79645
Adverse Effects	2490	.290	46996	<.001*	4760	.042	46660

a - d.f.=5, b - d.f.=1, c - d.f.=117, d - d.f.=4, e - d.f.=86
 *Tested against Inv x Treatment +Omitting Investigator 002
 All p-values are two-tailed except for the treatment effect which is one-tailed.

The results of the all patients cycle 1 means are shown in Table 63 (Table 7A, Sponsor's Analysis, Vol. 1.11, Appendix E, Pg 325). When compared to the evaluable patient's data shown in Table 61, no significant changes are apparent. Thus, one would predict that significant differences favoring nabilone would be found. This is indeed the case. Table 64 shows the results of the analysis of variance on the all patients cycle 1 data. Statistically significant differences favoring nabilone were observed on the following parameters: day 1 ($p = .007$) and average vomits ($p = .006$), day 1 ($p < .001$) and average nausea severity ($p = .001$), and investigator-rated efficacy ($p < .001$). The investigators also assigned a higher side effect incidence to nabilone ($p < .001$).

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Table 63
Cycle 1 - All Patients
Means

Drug	Investigator gator n	Freq. of Vomits		Severity Of Nausea		Food Intake		Investigator's Global Impressions		
		Avg.	Day 1	Avg.	Day 1	Avg.	Day 1	Efficacy	Adv. Effects	
Nabllone	001	9	5.27	5.22	2.07	2.00	0.69	0.78	3.00	1.22
	002	19	5.78	8.53	1.42	1.74	0.92	0.84	2.11	1.68
	003	2	11.17	23.50	1.33	2.00	0.50	2.50	2.50	1.50
	004	5	10.40	10.40	1.80	1.80	0.80	0.80	2.60	1.20
	005	23	3.74	3.74	0.83	0.83	1.30	1.30	2.05 ^b	1.14 ^b
	006	23	5.48	5.48	1.26	1.26	1.35	1.35	2.48	1.13
Composite	81	5.48	6.42	1.30	1.38	1.11	1.10	2.34 ^e	1.29 ^e	
Compazine	001	11	11.80	12.73	2.20	2.27	0.98	0.91	3.64	0.09
	002	19	8.02	9.68	1.83	2.21	0.79	0.79	3.32	0.11
	003	7	23.86	23.86	2.29	2.29	0.57	0.57	3.71	0.14
	004	7	21.40 ^a	21.40 ^a	2.86	2.86	0.43	0.43	4.71	0.00
	005	27	7.65 ^c	7.65 ^c	2.26	2.26	0.56	0.56	3.93	0.04
	006	21	9.13	10.85 ^d	2.00	2.19	0.89	0.81	3.52	0.05
Composite	92	10.77 ^f	11.66 ^f	2.15	2.28	0.72	0.70	3.72	0.07	

a_n=5, b_n=22, c_n=23, d_n=20, e_n=80, f_n=85

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Table 64:
 Cycle 1 - All Patients
 Analysis of Variance on The Ranks
 (Table 8, Sponsor's Analysis, Vol 1.11, Appendix E, pg 326)

	<u>Investigator</u>		<u>Treatment</u>		<u>P</u>	<u>Inv. x Treatment</u>		<u>Error</u> <u>S.S.c</u>
	<u>S.S.a</u>	<u>p</u>	<u>S.S.b</u>	<u>P</u>		<u>S.S.a</u>	<u>P</u>	
Freq. of Vomits - Average	22182	.077	13873	.006	18721	.134	352217	
- Day 1	27961	.027	13133	.007	18758	.126	346184	
Sev. of Nausea - Average	22292	.044	33984	.001	16220	.137	307421	
- Day 1	20275	.061	25874	.001	10435	.357	302378	
Food Intake - Average	14374	.246	4446	.075	11329	.383	343227	
- Day 1	11827	.342	4757	.066	11199	.374	334242	
Efficacy	12746	.215	53736	.001	10661	.313	284928d	
Adverse Effects	8293	.066	114377	.001	4468	.343	125810d	

Ad.f.f.=5, Bd.f.f.=1, Cd.f.f.=161, Qd.f.f.=160

All p-values are two-tailed except for the treatment effect which is one-tailed.

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Further, the results of the all patients' cycle 1 analysis are in general agreement with the antinauseant and antiemetic effect of nabilone demonstrated in the analysis of the evaluable patients who completed both cycles of the crossover. This finding tends to negate any suspicion of unintentional or systematic bias that may have been introduced by evaluating only patients who completed the crossover.

The results of the patient preference questions are tabulated and analyzed in Table 65 (Table 9B, Sponsor's Analysis, Vol 1.11, Appendix C, pg 330). Nabilone was preferred by evaluable patients (p .001) and all (evaluable and unevaluable) patients (p .001).

Table 65
Analysis of Patient Preference Frequencies

<u>Evaluable Patients</u>			
<u>Source of Variation</u>	<u>d.f.</u>	<u>x²</u>	<u>P</u>
Investigator x Cycle	5	2.63	.500
Treatment	1	28.13	.001
Inv. x Treatment	5	9.52	.090
<u>Evaluable and Unevaluable Patients</u>			
<u>Source of Variation</u>	<u>d.f.</u>	<u>x²</u>	<u>P</u>
Evaluability x Seq. Gp. 1	1	0.29	.500
Treatment	1	149.98	.001

Comments:

The composite results of the multicentered study of both the evaluable group and the cycle 1 all patients analysis provide persuasive evidence of a highly significant antinauseant and antiemetic effect of nabilone. The effect of nabilone of food intake is less striking.

The study was also analyzed by each component (investigator). Only 4 of 6 studies were analyzed statistically (#001, 002, 005 and 006). Studies 002, 005, and 006 were still in progress at the time of the NDA submission. We will ask the sponsor for all data as part of the safety update. The results are so impressive that I do not believe that further documentation of efficacy is necessary. However, the sponsor should be asked to subdivide the non-cisplatin based chemotherapies into their

respective groups and perform a categorical analysis of patient perceptions (nabilone better, same, placebo better). This may provide a useful analysis to answer our consultant's (Dr. Johnson) suggestion that the drug demonstrate efficacy against a wide variety of chemotherapy regimens, viz, DTIC-based regimens, Adriamycin-based regimens, Cytosan-based regimens without Adriamycin, and any other regimen occurring with such frequency as to make evaluation meaningful.

Investigator #002 (Einhorn) had a residual effect that invalidated the analysis of variance. However, the categorical analysis was performed in this study, highly significant results favoring nabilone were evident. If one accepts the categorical analysis in this study, then nabilone demonstrated efficacy in 4/4 analyzed centers. The results obtained in the other two centers were not analyzed due to the small numbers of evaluable patients. The data trends are in agreement with those of the 4 analyzed studies.

Again, as in all the studies reviewed, I have no doubt that the double-blind was not maintained due to the unmistakable psychotropic effects of nabilone. This does not, in my opinion, negate the study results.

Conclusion:

This adequate and well-controlled study demonstrates the efficacy of nabilone against the nausea and vomiting associated with cancer chemotherapy. Of equal importance, the studies involved a different patient population (see Table 58) than those who participated in the Einhorn trials which utilized active controls (Protocols 9 and 20). (Note: Einhorn's patients in Protocol 28 were not included in the vomiting frequency analysis. This removed 15 patients with testicular cancer, 12 patients with breast cancer, and 6 "other" patients from the analysis).

Overall conclusions:

The sponsor has demonstrated substantial evidence of the effectiveness of nabilone as an antiemetic adjunct in cancer chemotherapy regimen in both compazine- and placebo-controlled trials. The Einhorn studies in Protocols 9 and 20 demonstrate nabilone's effectiveness vis a vis compazine in these adequate and well controlled trials. The placebo controlled trial (28) had 3 of 4 centers demonstrating nabilone's superiority over placebo. The fourth of four placebo controlled trials demonstrated nabilone's superiority in the categorical data analysis.

Nabilone was fairly well tolerated by the study participants insofar as there was both numerical and statistical superiority favoring nabilone over compazine or placebo as the drug preferred by patients.

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There is sufficient evidence to recommend that nabilone be considered an effective antiemetic agent. A favorable benefit/risk judgment will require a supervisory overview as the safety review was done by a second reviewer, Dr. Hanson.

Tolerance to the subjective CNS effects of CESAME¹ (R) was noted in studies employing normal volunteers. A partial loss of tolerance occurred within one week after cessation of nabilone. I looked for signs of diminished drug effect in the clinical trials and didn't see any. It may not occur to any significant degree in the 1 to 4 mg/day dose range. Alternatively, tolerance may be offset by a decreasing emetic stimulus over a chemotherapy course. I also don't believe that tolerance will be a problem with repeat cycles of therapy as 3 to 6 week washout periods between cycles should restore full sensitivity, even if tolerance occurs within a chemotherapy cycle.

The abuse potential of nabilone has been evaluated in preclinical and clinical studies. My drug abuse evaluation of 11/23/82 reached several conclusions about nabilone: 1) it is pharmacologically similar to delta-9-tetrahydrocannabinol; 2) a substantial overlap exists between the antiemetic dose range and the dose range producing subjective effects; 3) it has a high potential for abuse; and 4) it should be controlled in the same schedule of the Controlled Substance Act as delta-9-tetrahydrocannabinol (Schedule II upon marketing approval). The Drug Abuse Advisory Committee recommended on April 28, 1983 that nabilone be scheduled in CSA Schedule III at the time of marketing approval. I am recommending that the Division reject the Committee's advice and propose nabilone for CSA II. Accordingly, I will draft the scheduling documents to propose a Schedule II classification of nabilone.

f. Labeling review:

The proposed labeling is, in many sections, unacceptable. I have specific recommendations for the labeling sections to be incorporated into the draft approvable letter (vide infra). These will be communicated to Drs. Tocus, Hanson, Katz and Leber in the formulation of the draft labeling.

g. Summary of recommendations:

(1) Scientific

- (a) Nabilone has demonstrated efficacy as an antiemetic against chemotherapy-induced nausea and vomiting. However, the unsubmitted data from the placebo-controlled study should be added to that previously submitted. A composite or individual (site) analysis of variance would be unnecessary

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although of interest. A categorical analysis of noncisplatin-based chemotherapy regimens should be conducted (Adriamycin-based regimens, DTIC-based regimens, and any other regimens which have sufficient data to allow a meaningful analysis) in order to demonstrate a salutary effect of nabilone on several major chemotherapy regimens.

(b) Nabilone should be considered for CSA Schedule II as its abuse potential is equal to that of delta-9-THC.

(2) Administrative

(a) Draft labeling and drafting of the anticipated Summary Basis of Approval be undertaken rapidly if and when the supervisory review makes a finding of favorable risk/benefit is found.

Frank J. Vocci Jr.
Frank J. Vocci, Jr., Ph.D.

CC:
NDA Orig
HFN-120
HFN-120/FVocci/10/12;11/29;12/6/84
FT:dcm/10/24;11/30;12/6;12/16/84
DOC #2138C

NDA 19677

1 OF 1

NDA

18-677

STATISTICAL

REVIEW

Statistical Review and Evaluation

Date: SEP 20 1982

NDA #: 18-677/Drug Class 1C

Applicant: Eli Lilly and Company

Name of Drug: Cesamet (nabilone)

Documents Reviewed: Volume, 1.10-1.15 (undated)

Medical Input: M. Milliken, M.D. (HFD-120). This review has been discussed with Dr. Milliken, who is in agreement with the conclusions.

The material reviewed consists of the results of four protocols in the treatment of nausea and vomiting in cancer patients undergoing chemotherapy. All four studies are double-blind randomized crossover trials; three utilized prochlorperazine (Compazine) as control treatment (protocols 7,9,20) while one (protocol 28) utilized a placebo control.

The studies are briefly described in Sections I-IV below, along with a summary of the primary efficacy results; section V summarizes the safety data.

I. Protocol 7 - Drs. Herman, Jones, and Bressler.

This study enrolled 43 patients from one hospital, of which 14 were excluded from efficacy evaluation ("due to protocol violations"). Chemotherapy was given in cycles of 1-5 days duration with 2-4 weeks between cycles. Table 9 gives the frequencies of the various daily doses utilized. Tables 1 and 2 summarize the types of cancer and chemotherapy involved.

The sponsor claims no statistically significant differences using nonparametric crossover analyses of frequency of vomits, severity of nausea, or food intake variables (all P-values for average scores and day 1 scores are greater than .10 in the sponsor's Table 4, page 149, volume 1.15). Also, no differences were seen in the frequency of patients with nabilone better as opposed to Compazine better in these variables (all P-values greater than .29, see Table 3).

II. Protocol 9 - Dr. Einhorn

This study enrolled 98 patients, of whom 83 met the efficacy evaluability criteria. Chemotherapy was given in cycles of 1-5 days duration with 2-4 weeks between cycles. Tables 1 and 2 summarize the types of cancer and chemotherapy involved. Table 9 gives the frequency of patients by daily dose.

Statistically significant differences in favor of nabilone were found at the .001 level from nonparametric crossover analyses for frequency of vomits, severity of nausea, and food intake using average scores from all days of treatment and also for comparisons of frequency of patients with nabilone better as opposed to Compazine better using day 1 only. See Table 3.

III. Protocol 20 - Drs. Young, Einhorn, Bressler

This protocol included three studies with a total of 126 enrolled, 75 of which were considered evaluable. Of the 51 unevaluable patients, 14 were due to protocol deviations and 37 due to "incomplete study" (23 of these 37 patients did not continue into the second cycle while 13 were incomplete due to the suspension of studies by the sponsor in 1979. Seven patients terminated early due to adverse experiences on nabilone compared to none on Compazine. Lack of efficacy was cited as the reason for early termination for three patients on nabilone, two on Compazine and two on both cycles. Chemotherapy was given in cycles of 1-5 days, with cycles 3-6 weeks apart. The dose of nabilone was one 2 mg capsule b.i.d. and the dose of prochlorperazine was one 10 mg capsule b.i.d. Tables 1 and 2 summarize the types of cancer and chemotherapy used.

The sponsor claims statistically significant differences in favor of nabilone at the 3% level of significance or less for all variables analyzed by a nonparametric crossover analysis (global efficacy and average and day 1 results for frequency of vomits, severity of nausea, and food intake). In addition, significantly more patients preferred the nabilone as opposed to the Compazine cycle. See Tables 4 and 5.

IV Protocol 28 - Six investigators

These studies enrolled 199 patients, of which 129 were considered by the sponsor to be "evaluable for efficacy." Placebo was utilized as control drug in these studies. Of the 70 "unevaluable" patients, 50 were listed as "crossover incomplete." The sponsor's Table 15 lists the reasons for 67 "early terminations." Leading causes were nabilone-related adverse experiences (22 patients) and lack of efficacy-placebo (12 patients). A total of eight patients who terminated early were considered evaluable - 6 of these were terminated due to lack of efficacy (placebo).

Chemotherapy was given in cycles of 1-5 days duration, with 3-6 weeks between cycles. The dose of nabilone was one 2 mg capsule b.i.d.

The sponsor claims statistically significant differences in favor of nabilone over placebo from crossover analyses of variance on ranks for frequency of vomits, severity of nausea, and food intake (both average value and day 1 only) and also for global efficacy (all p-values are given as less than .021). In addition, significantly more patients preferred the nabilone as opposed to the placebo cycle ($P < .001$). See tables 4 and 5.

V. Safety Data

Table 7 gives the percentage of patients in each study experiencing drowsiness, vertigo, dry mouth, and "high." Clearly the percentages for each adverse experience for nabilone are greater than for the control drug in each study.

Table 8 summarizes the data tabulated by the sponsor in regard to changes in blood pressure from baseline. These tabulations show that the increase in blood pressure for the control drug was greater in a large proportion of cases than the "increase" for nabilone.

VI. Reviewer's Comments

All four protocols included a large number of patients who were not analyzed in the sponsor's crossover analyses due to "protocol violations," incomplete crossover, etc. The sponsor has included analyses of cycle 1 for all patients which may be useful for investigating the effect of the numerous "unevaluable" patients. The results for Protocol 7 (page 154, volume 1.15) showed trends in favor of nabilone for all three variables analyzed (frequency of vomits, severity of nausea, food intake), but none were statistically significant at the 10% level (nor were the crossover analyses using only evaluable patients). The cycle 1 all patients analyses for these variables in protocol 9 (page 377 of volume 1.14) also showed agreement with the crossover analyses. The all patients analysis in protocol 20 produced a statistically significant difference in favor of nabilone for global efficacy ($P=.047$) but not for frequency of vomits, severity of nausea, or food intake. The lack of significant differences in this cycle 1 analysis is primarily a result of Investigator 301 showing no difference between nabilone and Compazine except for global efficacy. Investigator 302, on the other hand, produced *Einborn* significant results in favor of nabilone at the 5% level for frequency of vomits and severity of nausea in addition to global efficacy for the cycle 1 all patients analysis. The all patients cycle 1 analysis for placebo-controlled Protocol 28 (pages 326, volume 1.11) showed statistically significant differences at the 1% level in favor of nabilone for frequency of vomits and severity of nausea in addition to global efficacy and at the 10% level for food intake.

Tables 1 and 2 show that Protocol 7 had a different patient population than the other three protocols with regard to both types of chemotherapy and type of cancer (Hodgkins and lymphoma account for over 58% of the patients in Protocol 7 compared to only 8% in the other three protocols). No significant differences between nabilone and Compazine are claimed by the sponsor for Protocol 7 although the trends do favor nabilone consistently. Although Protocol 7 involved fewer patients than the other protocols reviewed, this reviewer estimated a power of approximately .77 in Protocol 7 for detecting a difference of the magnitude observed in Protocol 9 for the frequency analysis

of nausea severity using Gart's test with a two-sided .05 significance level (source: J. Cohen, Statistical Power Analysis for the Behavior Sciences, 1969).

Tables 3-6 indicate rather strong evidence of effectiveness for Protocols 9, 20, 28. The crossover analyses of response scores reported in Table 6 included appropriate tests for residual effects. The only residual effect significant at the 10% level (of those variables summarized in Table 6) is global efficacy in Protocol 20 ($P=.076$). Cycle 1 of Protocol 20 favored nabilone for global efficacy but only at a P -value of .243.

Koch's nonparametric crossover analysis was used in Protocols 9 and 11 while an analysis of variance, including an investigator term, was utilized in Protocols 20 and 28 on the ranks of the combined data. No references are cited to justify this latter procedure, although this general methodology has been investigated by Conover and Iman ("On some alternative procedures using ranks for the analysis of experimental designs." Communications in Statistics - Theory and Methods, A5(14), 1349-1368, 1976), but not for this specific situation. The overall results of the frequency data given in Table 4 support the results of the analyses of variance done on the ranks for Protocols 20 and 28. Although no combined analysis of the frequency data was attempted by the sponsor for either protocol, the sponsor's analyses by investigator showed statistically significant results in favor of nabilone for at least three of the four frequency variables for each of the three large studies (33-36 patients) in Protocol 28 and for one of the two large studies in Protocol 20 (investigator 302 - 36 patients). Although investigator 301 in Protocol 20 (32 patients) produced no significant results at the 5% level, results did strongly favor nabilone for severity of nausea ($P=.063$, two-sided), investigator's global impression of efficacy ($P=.054$, two-sided) and patients preference ($P=.13$, two-sided). The patient preference data in Protocols 20 and 28 also statistically favors nabilone (see Table 5).

Table 7 shows a clear increase in adverse experiences for nabilone compared to Compazine. The blood pressure information presented by the sponsor (summarized in Table 8) indicates that nabilone lowers blood pressure but does not give any information about the magnitude of the blood pressure decreases experienced by patients on nabilone. We calculated a median decrease from baseline in daily average blood pressure of 18 mmHg for standing systolic blood pressure for investigator 5 in protocol 28. (Table 8 suggested that this protocol produced the largest frequency of blood pressure declines on nabilone). This same variable in protocol 9 produced a median decrease of 9.6 mmHg. It may be possible that the Compazine control in protocol 9 (which tended to increase blood pressure) may have affected the blood pressure decreases on nabilone during the second cycle. We calculated a median decrease on nabilone during cycle 1 of this study (which would be unaffected by the Compazine cycle) of 14.8 mmHg. The maximum decrease in blood pressure for a patient using nabilone (as opposed to the average decrease during nabilone treatment) might also be of value, but this variable was not tabulated by the sponsor.

Conclusions

Three of the 4 protocols reviewed produced statistical evidence of efficacy for nabilone compared to Compazine (Protocols 9, 20) and placebo (Protocol 28). Trends favoring nabilone over Compazine were present in the remaining study (Protocol 7). The statistical efficacy results are summarized in Tables 3-6. Of concern is the large number of unevaluable patients in these studies. Analyses of cycle 1 for all patients, however, in general support the crossover analyses.

There is clearly an increased incidence of adverse experiences on nabilone (drowsiness, dizziness, "high", dry mouth - see Table 7). The data presented by the sponsor shows that nabilone decreases blood pressure from baseline but no attempt was made to quantify the magnitude of the decrease. We calculated a median decrease from baseline in daily average standing systolic blood pressure of 18 mmHg for investigator 5 in protocol 28 as an illustration of the magnitude of decreases experienced.

S. Edward Nevius
S. Edward Nevius, Ph.D.
Mathematical Statistician

cc:
Orig. NDA 18-677
HFD-120 HFD-120/Dr. Milliken
HFD-180/Dr. Lisook
HFD-232/Dr. Dubey
✓ HFD-232/Dr. Nevius
chron
File: DRU 1.3.2 NDA
ENevius/x34594/pak/rb/9/17/82 #0014r

Concur: Dr. Pledger *JP 7/17/82*
Dr. Dubey *D 9/17/82*

Table 1

Type of Cancer*

Cancer	Protocol 7		Protocol 9		Protocol 20		Protocol 28	
	Number of Patients	Percent	Number of Patients	Percent	Number of Patients	Percent	Number of Patients	Percent
Testis	1	3.4	68	81.9	24	32.0	18	14.0
Hodgkins	10	34.5	2	2.4	2	2.7	5	3.9
Lung	0	0	0	0	16	21.3	23	17.8
Breast	3	10.3	0	0	8	10.7	37	28.7
Ovary	0	0	3	3.6	0	0	15	11.6
Lymphoma	7	24.1	3	3.6	3	4.0	8	6.2
Other	8	27.7	7	8.5	22	29.3	23	17.8
Total	29	100	83	100	75	100	129	100

*Evaluable patients

Table 2

Type of Chemotherapy*

Number of Patients

Study	Number of Patients	
	Cis-Platinum and Other Combinations	Other Combinations with Cis-Platinum
Protocol 7	4	25
Protocol 9	75	8
Protocol 20	44	31
Protocol 28	45	84

w/ other

*Evaluable patients

Table 3

Comparison of Best Treatment Cycles
Protocols 7 and 9

	Frequency of Vomiting - Average			P-value (2-sided)	Frequency of Vomiting - Day 1			P-value (2-sided)
	Nabilone Better	Compazine Better	Same		Nabilone Better	Compazine Better	Same	
Protocol 7	14	10	4	.297	13	4	11	.436
Protocol 9	62	14	7	<.001	51	8	24	.002
Total	76	24	11		64	12	35	

	Severity of Nausea - Average			P-value (2-sided)	Severity of Nausea - Day 1			P-value (2-sided)
	Nabilone Better	Compazine Better	Same		Nabilone Better	Compazine Better	Same	
Protocol 7	13	7	9	.410	10	13	6	>.5
Protocol 9	52	14	15	<.001	28	35	18	.208
Total	65	21	24		38	48	24	

	Food Intake - Average			P-value (2-sided)	Food Intake - Day 1			P-value (2-sided)
	Nabilone Better	Compazine Better	Same		Nabilone Better	Compazine Better	Same	
Protocol 7	12	8	11	.402	11	13	5	>.5
Protocol 9	40	11	30	<.001	24	43	14	.167
Total	52	17	41		35	56	19	

Table 4

Comparison of Best Treatment Cycles
Protocols 20 and 28

	Frequency of Vomiting - Average		Frequency of Vomiting - Day 1*	
	Nabilone Better	Same	Nabilone Better	Same
Protocol 20 (Compazine control)	42	9	28	38
Protocol 28 (Placebo control)	97	10	73	49
	Severity of Nausea		Food Intake	
	Nabilone Better	Same	Nabilone Better	Same
Protocol 20 (Compazine control)	35	27	31	30
Protocol 28 (Placebo Control)	85	32	53	62
Investigator's Global Impressions of Efficacy				
	Nabilone Better		Control Better	
Protocol 20 (Compazine Control)	47		19	
Protocol 28 (Placebo Control)	98		18	

*"Best" treatment required to have at least 50% less vomiting.

Table 5

Patient Preference Frequencies

	<u>Prefer Nabilone</u>	<u>Prefer Control</u>	<u>No Preference</u>	<u>P-value</u>
Protocol 20 (Comazine Control)	55	15	5	<.001
Protocol 28 (Placebo Control)	99	15	15	<.001
<i>add ADR's, well</i>				
Prot 78	12 +1 11 +1 11 +1 17	+5 +1 +3 +2 +4 +1 +7 +4 +7	<i>✓</i> DWS	
ADR's from well	10x +2 12 13 118		<i>DR-6</i> Nat +2	<i>Plax</i> +4
Prot 20	+1 13 59	+5 +1 +4 +2 28		
Other	+6 +1 79	+1 29		
			95	

Table 6

Results of Sponsor's Crossover Analyses
on Response Scores

Variable	P-values by Protocol*		
	Protocol 7	Protocol 9	Protocol 20
Frequency of vomiting - Average	.108	<.001	.007++
Day 1	.150	<.001	.027++
Severity of Nausea - Average	.178	<.001	.007
Day 1	.271	.074	.024
Food Intake - Average	.157	<.001	.012
Day 1	.127	.136	.018
Investigator's Global Impression of Efficacy	--	--	<.001

+ Omitting Investigator 002 due to residual effect x investigator interaction. Tested against investigator x treatment due to significant interaction.

++Omitting investigator 306 due to residual effect x investigator interaction.

* P-values for Protocol 28 (placebo control) are one-sided, others (Compazine control) are two-sided but favor nabilone.

Table 7

Adverse Experiences[†] Tabulated by the Sponsor
Crossover Studies (Not including open label periods)

Adverse Experience	Study	Mabilone		Prochlorperazine	
		No. of Patients	Percent	No. of Patients	Percent
Drowsiness	Protocol 7	38	88.4	22	59.5
	Protocol 9	84	87.5	68	73.9
	Protocol 20	43	38.7	18	17.5
	Protocol 28	96	52.5	(9)**	5.5)
Vertigo or Dizziness	Protocol 7	36	83.7	11	29.7
	Protocol 9	70	72.9	34	37.0
	Protocol 20	41	36.9	8	7.8
	Protocol 28	102	55.7	(8)**	4.8)
"High"	Protocol 7	18	46.5	1	2.7
	Protocol 9	48	50.0	7	7.6
	Protocol 20	29	26.1	4	3.9
	Protocol 28	3*	1.6	(0)**	.0)
Dry Mouth	Protocol 7	33	76.7	8	21.6
	Protocol 9	3	3.1	1	1.1
	Protocol 20	18	16.2	2	1.9
	Protocol 28	57	31.1	(2)**	1.2)
At least one adverse experience	Protocol 7	43	100	35	94.6
	Protocol 9	90	93.8	74	80.4
	Protocol 20	88	79.3	45	43.7
	Protocol 28	160	87.4	--	--

[†] Includes both "drug-related" and "unknown"

* 17 patients in this protocol (9.3%) reported "euphoria". Sponsor comments that patients were not specifically asked about "high" as they were in the other 3 protocols.

**Placebo control

Table 8
Blood Pressure Analysis

Variable	Study	Nabilone		Between Treatments	
		No. of Patients with Decrease	Increase	Increase in blood pressure Nabilone < Control	Control < Nabilone
Recumbent Systolic	Protocol 7	16	9	10	2
	Protocol 9	44	38	48	24
	Protocol 20	30	34	29	15
	Protocol 28	79	21	55	16
Recumbent Diastolic	Protocol 7	12	11	8	3
	Protocol 9	47	29	41	31
	Protocol 20	27	33	23	18
	Protocol 28	51	27	37	19
Standing Systolic	Protocol 7	11	9	9	3
	Protocol 9	59	17	50	20
	*Protocol 20	31	19	25	8
	*Protocol 28	83	13	58	11
Standing Diastolic	Protocol 7	13	7	7	6
	Protocol 9	51	25	48	22
	*Protocol 20	28	21	20	13
	*Protocol 28	54	21	40	14

*These results were all labeled "standing systolic" by the sponsor.

MEMORANDUM OF CONSULTATION

DATE: May 16, 1985

BETWEEN: R. Katz, M.D. (HFN-120)
Division of Neuropharmacological Drug Products

AND: S. Edward Nevius, Ph.D. (HFN-713)
Statistical Evaluation and Research Branch
Division of Biometrics

SUBJECT: NDA 18-677 (Cesamet)

Our discussion centered on reanalysis of Protocol 28 excluding the results of Investigator 5 (Dr. Levitt). This was a 6-investigator placebo-controlled study of Cesamet in the treatment of nausea and vomiting in cancer patients undergoing chemotherapy. Dr. Levitt accounted for 58 of the 199 patients enrolled. The investigators contributing the next largest sample sizes were Drs. Gunnell (45 patients) and Einhorn (42 patients).

A major problem in reviewing protocol 28 had been the large number of unevaluable patients. In consultation with Dr. Cheung of HFN-120, I had previously adjusted the sponsor's analysis of patient preferences in this crossover study by first classifying unevaluable patients who had not completed the crossover due to adverse reactions or lack of efficacy as a preference for the alternate therapy and then also including preferences listed for patients considered as unevaluable for other reasons. My memorandum dated November 8, 1983, stated that 118 patients preferred Cesamet compared to 42 patients who preferred placebo using this technique. A strong preference for Cesamet is still present if we omit the Levitt patients (85 prefer Cesamet, 32 prefer placebo).

Another approach used previously to address the problem of unevaluable patients was to analyze only the first period of the crossover. A blocked Wilcoxon test omitting the Levitt patients produced 2-sided p-values less than .001 for both global efficacy and severity of nausea and $p=.07$ for frequency of vomiting, all favoring Cesamet over placebo.

I mentioned that Dr. Einhorn had been involved in all 3 studies which showed a significant difference between Cesamet and the control drug. Einhorn was the sole investigator in Compazine-controlled Protocol 9 and the primary contributor to the significant difference found in Compazine-controlled Protocol 20 as well as being an investigator in Protocol 28. I noted, however, that the Gunnell clinic also contributed strongly to the efficacy findings in Protocol 28 - a significant difference was seen at the 5% level for the period 1 analysis in the Gunnell clinic for global efficacy and severity of nausea as well as for the patient preferences adjusted for dropouts as explained above. Thus the efficacy analyses do not entirely rest on one investigator.

I remarked that I had had consultations with Drs. Cheung and Vocci since my original 9/20/82 review was issued in addition to performing the above analyses; subsequent consultations have not, however, altered my original conclusions concerning the efficacy of Cesamet.

S. Edward Nevius

S. Edward Nevius, Ph.D.
Mathematical Statistician

cc: Orig. NDA 18-677
HFN-120
HFN-120/Dr. Katz
HFN-120/Dr. Vocci
HFN-120/Dr. Leber
✓ HFN-713/Dr. Dubey
HFN-713/Dr. Nevius
Chron.
File: DRU 1.3.2 NDA
SEnevius/pls/njs/05/21/85/34584/#1378r

MEMORANDUM OF CONSULTATION

DATE: November 8, 1983

BETWEEN: W. Cheung, M.D. (HFN-120)
Division of Neuropharmacological Drug Products

AND: S. Edward Nevius, Ph.D. (HFN-713)
Statistical Evaluation Branch
Division of Biometrics

SUBJECT: NDA 18-677 (Cesamet)

Our discussions involved 3 points of concern in this NDA: (1) the affect of the large number of unevaluable patients on the efficacy results, (2) the effects of the different chemotherapeutic agents on the efficacy results, and (3) documentation of hypotension in patients on Cesamet in the studies.

(1) Our September 20, 1982, statistical review utilized the results of the sponsor's "cycle 1 all patients" analyses to conclude that the large number of unevaluable patients did not alter the general conclusions of the sponsor. These analyses treated the first period of the crossover studies as a parallel study and included a much larger patient population. Dr. Cheung approached this problem by tabulating for each study the number of patients with adverse reactions and lack of efficacy who were listed as "unevaluable" and classifying them as a preference for the alternate therapy. In addition, she included the preferences of other patients listed as unevaluable.

I added these figures to the sponsor's tabulations of patient preferences. Strong preferences for Cesamet compared to control are still evident - 66 preferring Cesamet compared to 29 preferring Compazing in protocol 20, 118 preferring Cesamet compared to 42 preferring placebo in protocol 21. Statistical significance is present even if we consider the 2 primary investigators in protocol 20 separately - Investigator 301 (Dr. Young), 28 preferring Cesamet compared to 15 preferring Compazine (two-sided $p < .05$, McNemar Test); Investigator 302 (Dr. Einhorn), 26 preferring Cesamet compared to 12 preferring placebo (two-sided $p < .05$, McNemar Test).

(2) Dr. Cheung's tabulations of patient preferences according to chemotherapeutic agents show no evidence that efficacy depends on the primary or secondary chemotherapeutic agent utilized. No further statistical analysis appears warranted.

(3) Our September 20, 1982, review indicated that Cesamet decreased blood pressure. Dr. Cheung investigated the clinical importance of these blood pressure decreases by defining hypotension as either a 20 mmHg decrease from recumbent to standing systolic blood pressure along with a systolic standing blood pressure of 90 mmHg or less or a systolic blood pressure of 90 mmHg in either the standing or recumbent position. Dr. Cheung's tabulations

showed the majority of cases of hypotension occurred in patients from investigator 302 in protocol 20 and investigator 2 in protocol 28 - in both cases the investigator is Dr. Einhorn. Dr. Einhorn's studies appeared to have the most complete blood pressure follow-up data available.

In Dr. Einhorn's protocol 20 study, there were 7 patients with hypotension on Cesamet only, 1 on Compazine only, and 3 on both (two-sided $p=.04$, McNemar Test). In Dr. Einhorn's protocol 28 study there were 10 cases of hypotension on Cesamet only, 1 on placebo only, and 2 on both (two-sided $p=.007$). These p-values are actually conservative because (1) in protocol 20, 2 additional patients had hypotension on Cesamet but had no readings on Compazine and 1 of the patients with hypotension on both had a clinically worse case on Cesamet (per Dr. Cheung) and (2) in protocol 28, 2 additional patients had hypotension on Cesamet but no blood pressure readings on placebo and 1 of the patients with hypotension on both had a clinically worse case on Cesamet (per Dr. Cheung). (No patients were found with hypotension on the control but no readings on Cesamet).

S. Edward Nevius
S. Edward Nevius, Ph.D.
Mathematical Statistician

cc: Orig. NDA 18-677
HFN-120
HFN-120/Dr. Cheung
HFN-713/Dr. Dubey
✓ HFN-713/Dr. Nevius
Chron.
File: DRU 1.3.2 NDA
SEnevius/PLT/RB/11/14/83/34594/0582r

BIO/DISSOLUTION

REVIEW

~~CONFIDENTIAL~~

FOI

LOG OUT

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

87

DATE : OCT 24 1985

TO : Paul D. Leber, M.D.
Director, Division of Neuropharmacologic
Drug Products HFN-110

Through: Henry J. Malinowski, Ph.D.
Acting Director
Division of Biopharmaceutics HFN-220 *HJM*

FROM : Paul L. Hepp, Pharm.D.
Acting Chief,
Pharmacokinetics Evaluation Branch HFN-226

SUBJECT: Nabilone (Cesamet) NDA 18-677

Based upon an October 15, 1985 letter from the firm it is indicated that the 2 mg rotary evaporated capsule was the product which underwent phase III clinical trials. You have confirmed that it was the studies within phase III on which safety and efficacy evaluation has been made and that earlier clinical trials which utilized the 1 mg process are not pivotal for safety and efficacy evaluation.

The formulations of the 1 and 2 mg capsules by either the process are as follow:

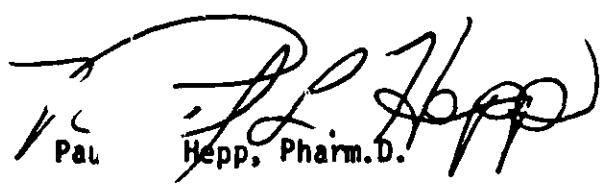
<u>Ingredient</u>	<u>1 mg capsule</u>	<u>2 mg capsule</u>
Nabilone	1 mg	2 mg

The Division believes that the differences in the 1 and 2 mg capsule formulation in terms of ingredients as well as the processes are not significantly different and would not be expected to lead to any important differences in bioavailability. However, only a pilot type (4 subjects) bioequivalency study exists and the results do not allow a determination of bioequivalency. Comparative dissolution data could possibly be adequate to imply bioequivalence if dissolution for the two test products compared to each other was similar.

Comparative dissolution data using the interim method indicate that mean dissolution at 60 minutes was somewhat slower for the capsule than for the 1 mg capsule than for the 1 mg

Additionally, dissolution data generated early on by the firm using a method which was not adopted indicated slower mean dissolution for the capsule than for the

Due to the fact that dissolution for the is somewhat slower in and slower still in than the , it is difficult to conclude bioequivalence without an adequate bioequivalency study. Therefore, a comparative dissolution approach does not appear feasible and a bioequivalency study between the is necessary if bioequivalence is to be determined. A clinical judgement to assess the possible clinical implications (safety/efficacy) of the lack of proven bioequivalency is necessary to determine when the bioequivalency study should be conducted (ie deferral to phase IV or pre-approval). One possible option may be to allow the firm to market the until the bioequivalency study has been conducted.


Paul Hepp, Pharm.D.

Nabilone
1 mg Capsules
Cesamet
NDA 18-677
1-0
Wang #5681x

Eli Lilly
Indianapolis, Indiana
Submission Dated:
October 15, 1985

JAN 21 1986

Review of Submission

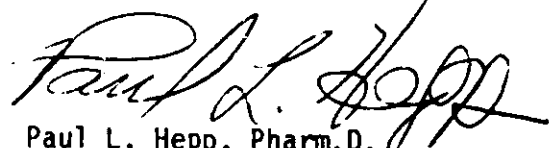
The firm has included the following information within the subject submission:

- "- We plan to market a 1 mg dosage form of Cesamet. Should FDA interest be sufficient, we could also provide for the marketing of a 2 mg dosage form.
- Our dose proportionality study was conducted with the 1 mg dosage form. Our initial clinical trials were also conducted with this formulation.
- We conducted a crossover biopharmaceutics study comparing dosage forms. Our conclusions were that the forms are equivalent.
- Our Phase 3 clinical trials were conducted with the 2 mg dosage form."

The submission also included a synopsis of the process (Appendix 1).

Recommendation:

This submission has been noted by the Division of Biopharmaceutics and the issues addressed in the Division's October 24, 1985 memo to Dr. Leber. It should be noted that now the firm will market the 1 mg tablet. No further action is required by the Division of Biopharmaceutics.


 Paul L. Hepp, Pharm.D.
 Pharmacokinetics Evaluation Branch

RD Initialed by C.T. Viswanathan, Ph.D.
 FT Initialed by C.T. Viswanathan, Ph.D. *CTV* 11/7/86

cc: NDA 18-677 orig., HFN-120, HFN-226(Hepp), Chron, Drug, and FOI Files.

PLH:smj:kek:5681x (1-14-86)

END

A handwritten signature in black ink, consisting of several loops and a long tail stroke, positioned above a horizontal line.

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011