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NDA 18-651

Unimed Incorporated
Attention: Mr. Paul Bollenbacher
35 Columbia Road
Somerville, New Jersey 08876

MAY 31 1985

Dear Mr. Bollenbacher:

Please refer to your firm's new drug application dated June 24, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation MARINOL (dronabinol) Capsules, and to the agency's 'approvable' letter dated May 2, 1985.

We also acknowledge receipt of your amendments (2) dated May 16, 1985, which include a safety update, final printed labeling, introductory promotional materials, and patent information.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling, provided that the NDC codes throughout your labeling are corrected to utilize the "4-4-2" digit configuration, beginning with your assigned code number "0051-." Accordingly, the application is approved.

However, we object to your proposed introductory advertising materials which prominently identify MARINOL as THC. We are concerned that this marketing approach may increase the risk of diversion and abuse of MARINOL. In our view, prominent identification of MARINOL as THC is totally unnecessary to promote its use as an antiemetic and antinauseant. Consequently, any advertising of your product should refer to it as "MARINOL", and/or as dronabinol, the official non-propriety name adopted by the USAN council. Eliminate completely any advertising use or reference to "THC."

We recognize that the approved product labeling identifies common alternative, but unofficial, names for dronabinol. This was permitted solely to inform responsible physicians about the origins of the product. Clearly, the use of THC in this context is quite different from its use in your proposed campaign. Additional comments upon your advertising campaign may be forthcoming from the Division of Drug Advertising. They are currently reviewing your submitted materials and will contact you when their review is completed.

Approval is granted with the explicit condition that any remaining issues regarding validation will be promptly and satisfactorily resolved.

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

Please submit one market package(s) of the drug when available.

NDA 18-651

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We remind you that you must comply with the requirements set forth under 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

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Summary Basis of Approval

NDA 18-651

Applicant:
Unimed Inc.
35 Columbia Road
Somerville, New Jersey 08876

Drug Generic Name:
dronabinol (also known as: delta-9-
tetrahydrocannabinol, THC)

Drug Trade Name:
MARINOL

I. Indications for Use:

MARINOL is 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 patients treated with MARINOL can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents.

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

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

Evidence supporting the efficacy of MARINOL in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from a variety of sources. The most persuasive evidence was obtained in subjects being treated with MOPP for Hodgkin's and non-Hodgkin's lymphomas. Other evidence supports the conclusion that MARINOL is effective against nausea and vomiting induced by other cancer chemotherapy regimens employed in the treatment of a wide variety of tumor types.

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

Oral, soft gelatin capsules (2.5, 5.0 and 10.0 mg). MARINOL is best administered at an initial dose of 5 mg/M² given 1-3 hours prior to the administration of chemotherapy, then every 2-4 hours thereafter for a total of 4-6 doses/day. The dose may be slowly increased to a maximum of 15 mg/M² in the absence of significant adverse reactions at lower doses, but this should be done with caution, as the incidence of disturbing psychological reactions increases markedly at this dose.

III. Manufacturing and Controls:

A. Manufacturing and Control

The description of the synthesis of dronabinol is provided in sufficient detail to establish the validity of the assigned chemical structure and confirm the suitability of the specifications and test methods for the bulk drug substance. The preparation of dronabinol consists entirely of a synthetic process. Adequate information is provided to explain each step of the process and the organic chemical reactions are reasonable for this type of compound. Raw materials and intermediates are satisfactorily identified and characterized, and sufficient detail is given to the isolation and purification of dronabinol.

The finished product manufacturing and controls procedures for MARINOL are adequately described and sufficient to characterize the product and assure its identity, strength, quality and purity.

B. Stability Studies

The stability data for MARINOL capsules support the proposed expiration date of twenty-four (24) months for the product in amber glass bottles with plastic caps.

C. Methods Validation

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed - but is ongoing in our laboratories. In such a case the policy of the National Center for Drugs and Biologics is to proceed with approval.

D. Labeling

The immediate container label and carton label for capsules in the bottles are in compliance with the technical requirements pertaining to the following: proprietary name, ingredient statement, control number, expiration date, prescription caution, applicant's name and address, storage statement, and net contents statement.

The accompanying package insert is also satisfactory under the "DESCRIPTION" and "HOW SUPPLIED" sections. Insofar as could be determined from a thorough search of available publications, the trade name is not in conflict with a name of any other drug.

E. Establishment Inspection

Verification has been provided that the operations of the facilities involved in the manufacture of the new drug substance, and in capsuling and packaging the finished dosage form, are in compliance with CGMP regulations.

The applicant's facilities are registered.

F. Environmental Impact Analysis Report

The applicant provided information that the product and its production will have no adverse impact on the environment. The disposal of wastes generated in manufacturing facilities is controlled in accordance with appropriate local, state and federal regulations.

IV. Pharmacology:

- A. MARINOL contains delta-9-tetrahydrocannabinol which is a biologically active alkaloid found in the plant Cannabis sativa. The initial antiemetic activity was reported by cancer patients who smoked cannabis (marijuana) cigarettes obtained illegally. The mechanism of antiemetic action of MARINOL is not known.
- B. Acute toxicity studies of delta-9-THC, delta-8-THC and crude marijuana extract (CME) were performed in rats, dogs and monkeys. Signs of toxicity were similar for all three compounds and included inactivity, hypersensitivity to touch, ataxia, catatonia, severe hypothermia (30-60% decrease), decreased respiratory rate and generalized body twitching. Death appears to be associated with respiratory arrest.

Median Lethal Dose Levels for delta-9-
and delta-8-THC and CME

<u>Rat Strain</u>	<u>Compound</u>	<u>Route</u>	<u>Purity</u>	<u>Vehicle</u>	<u>Sex</u>	<u>LD50 in mg/kg (95% CL)</u>
Fisher	Delta-9-THC	p.o.	96%	sesame oil	M	1015 (780-1320)
			90%	2.5% ETOH in S.O.	F	800 (630-1010)
	i.v.	90%	2.5% Tween 80 in saline	M	1910 (2790-2680)	
		90%	2.5% Tween 80 in saline	F	1040 (820-1320)	
	Delta-8-THC	p.o.	99%	2.5% ETOH in S.O.	M	1980 (1580-2470)
			99%	2.5% Tween 80 in saline	F	860 (680-1090)
CME	p.o.	a	sesame oil	M	3300 (2480-4390)	
				F	1380 (950-2020)	
Wistar- Lewis	delta-9-THC	p.o.	90%	2.5% ETOH in S.O.	M	1160 (850-1582)
					F	860 (640-1160)

- a. CME contained: 32% delta-9-, 2% delta-8-THC, 2.9% cannabidiol, 3.5% cannabiol and 4% ethanol.

A comparison of the oral with intravenous toxicity revealed that MARINOL and the other tested cannabinoids are approximately 40-60 times more toxic when administered intravenously.

Subacute studies (5 days, p.o.) done in rats for delta-9, delta-8-THC (both 62.5-1000 mg/kg), and CME (187.5-3000 mg/kg) showed that the pharmacotoxic signs seen for these three compounds were essentially similar to that observed in acute studies for this species. A dose of 250 mg/kg for delta-9- and delta-8-THC, and 750 mg/kg for CME was found to be well tolerated in these animals. Again, mortality was due to CNS and respiratory depression. However, an important pharmacological sign did emerge from these five-day studies. Tolerance was evidenced with either decreased severity of effects or increased rate of recovery. Tolerance was found to develop on the third day of the treatment. Pathological findings obtained in these studies indicated the involvement of bone marrow and spleen, (delta-9- and delta-8-THC, above 500 mg/kg; CME, above 750 mg/kg). For delta-8-THC, additional pathological findings were observed; they were degeneration of seminiferous tubules and necrosis and mineralization of adrenal cortex. Weight gain depression occurred in these studies and organ weight changes included increases in adrenal and liver weights and a decrease in spleen weight.

A seven-day (p.o.) study carried out in monkeys with delta-9- and delta-8-THC (both up to 5 gm/kg) also indicated the emergence of tolerance in this species. Pharmacotoxic signs other than those seen in rats were persistent anorexia and temporary constipation. Similar to the rat studies, bone marrow hypocellularity was observed. Drug absorption seemed to present a greater problem in this species than in the rats since no further increases in pharmacological effects were observed as the dose of delta-8- and delta-9-THC was increased up to 5 gm/kg/day. No mortality occurred at this high dose level. Clearly, tolerance could only account for part of the observations obtained.

Subacute and chronic studies done in rats (delta-9-THC, 2-500 mg/kg; delta-8-THC, 50-500 mg/kg; and CME, 150-1500 mg/kg orally) showed that the three cannabinoids displayed qualitatively similar signs of toxicity. The general pattern was a biphasic one, i.e., initial CNS depression including hypothermia, hypopnea, inactivity, drowsiness, sedation, wide stance, hypersensitivity to touch, ataxia and weight gain depression to which tolerance developed in the first week or so; thereafter the central depression was replaced by CNS stimulation as evidenced by hyperactivity, irritability, development of fighting behavior, tremor and convulsion. Fighting behavior occurred in cyclic fashion and was inversely dose related. Tremor and convulsion occurred at high dose levels and were dose and treatment duration related. Tolerance to convulsion was not seen. The weight gain depression was persistently seen throughout the chronic studies and was initially associated with a normal or slightly decreased food

intake. Hypopnea lasted for up to 4 months of drug administration; thereafter the degree of hypopnea decreased. Hypocellularity of bone marrow and spleen as well as necrosis and vacuolization of the adrenal cortex were found in rats treated subchronically and chronically with high levels of these cannabinoids (delta-9 and delta-8-THC, above 250 mg/kg; CME, above 400 mg/kg). No such pathological changes were observed with delta-9-THC at doses below 50 mg/kg. For delta-8-THC and CME, additional pathological changes involving degeneration of seminiferous tubules occurred. The hypocellularity seen in the bone marrow and spleen might be related to the immunosuppressive responses reported for these cannabinoids. Organ weight changes included a consistent increase in adrenal weight and a decrease in pancreas, pituitary and uterus weight in general. Clinical chemistry revealed elevations in serum SGOT, SGPT, glucose, hematocrit and red blood cell count in the delta-9-THC treated animals. The significance of these changes is not clear since no concomitant pathological findings were observed.

A reproduction study performed by IBT, in rats utilizing doses of 0, 0.5, 1.5 and 5 mg/kg of delta-9-THC by gavage, showed little effect on the number of corpora lutea, implantation sites, resorption sites and viable fetuses, although pharmacological signs indicative of adequate dosing were observed in adult rats. At lactation day 12 and at weaning, a decrease in survival in medium and high dose offspring was observed (Control- 75%, MD- 69%, HD 55% on Day 12; Control- 67%, MD- 57%, HD- 55% at weaning)

Teratology studies in rats (0, 5, 15 and 50 mg/kg) and rabbits (0, 0.5, 1.5, 5.0 and 15.0 mg/kg) treated orally with delta-9-THC showed no significant teratogenic effects. Three HD fetuses in the rabbit study showed external abnormalities such as talipomanus and one of the three had multiple anomalies including spina bifida, unicorn, and acrania. Pup weight and survival in all studies was within normal limits.

MRI reproduction and teratology studies were performed at higher dose levels (12.5-50 mg/kg in rats; 50-600 mg/kg in mice) than the IBT studies. The results obtained, support the lack of teratogenic effects found in the IBT study. At these higher dose levels (12.5-50 mg/kg in rats, 50-600 mg/kg in mice), however, delta-9-THC caused a decrease in the number of viable pups, an increase in fetal mortality and an increase in early resorptions (as low as 5mg/kg in mice). A decrease in pregnancy rate and uterine weights was also observed.

In A/J mice, delta-9-THC (240 mg/kg) was shown to increase the frequency of orofacial anomalies (cleft palate, cleft lips and open eyelids) but it did not induce new type(s) of fetal anomalies.

In male rats treated orally for 77 days, delta-9-THC (5-25 mg/kg) caused a decrease in ventral prostate weights, epididymal weights, seminal vesicle weights and seminal fluid volume. At 25 mg/kg, it produced an area of sparse Leydig cells in the interstitium of testis, also a decrease in spermatogenesis and in the number of developing germ cells in the seminiferous tubules. It did not, however, affect sperm count, serum testosterone, mating success and offspring weight. It appeared that sufficient areas of normal Leydig cells remained to allow for production of normal levels of testosterone and for performance of normal reproductive function.

Acute cytogenic studies done with bone marrow of Sprague Dawley rats indicated that delta-9-THC (50 mg/kg) caused no significant changes in the frequency of chromosome aberration and mitotic index. delta-9-THC (0.2 and 1 mg/plate) did not produce any significant change in the reversion rates of S. typhimurium.

No carcinogenicity studies were submitted. MARINOL is approved only for short term use as an antiemetic in cancer patients undergoing chemotherapy who are unresponsive to conventional antiemetics. Carcinogenicity testing is not needed because exposure is short and because the drug is indicated in a patient population exposed to cancer chemotherapeutic agents with greater mitogenic and carcinogenic potential than MARINOL.

The pharmacology and toxicology of MARINOL has been characterized sufficiently to support the short term use of this drug as an antiemetic for patients undergoing cancer chemotherapy.

V. Medical:

A. Background

The active ingredient in MARINOL is dronabinol, the primary psychoactive cannabinoid found in Cannabis sativa (marijuana). Its mechanism of anti-emetic action is unknown, though it is presumed to exert this effect primarily through the central nervous system. Interest in this compound as an anti-emetic resulted from reports that patients experiencing nausea and vomiting from cancer chemotherapy received significant relief from these distressing symptoms after smoking marijuana. In addition to being active as an anti-emetic, dronabinol is capable of producing the full range of well-known psychic effects of marijuana, including changes in perception, affect, memory, and judgement.

B. Well-Controlled Studies Demonstrating Effectiveness**1. Kluin-Nelemans Study.****a. Design:**

This was a double-blind randomized placebo controlled crossover study of dronabinol given orally in twelve patients who received MOPP chemotherapy for Hodgkin's and non-Hodgkin's lymphoma. Patients ranged in age from 20-53, with a median age of 34.6 years. Each patient received daily oral doses of procarbazine and prednisone for 14 days. On days 1 and 8 each was given chloromethine and vincristine intramuscularly. Ten mg/M² of THC was given on days 1 and 8, two hours prior to chemotherapy, then four and eight hours after. Each patient was given six cycles of MOPP chemotherapy and patients were randomized to one of 4 sequences: (1) THC-PBO-THC; (2) PBO-THC-PBO; (3) THC-THC-PBO; or (4) PBO-THC-THC.

b. Efficacy variables:

Patients were rated according to a five (5) point scale defined in relation to their responses to previous courses of chemotherapy.

- (1) No improvement, no change compared to former courses.
- (2) Some improvement, vomiting and nausea of shorter duration or less vehement.
- (3) Pronounced improvement, although still vomiting and nausea.
- (4^A) Very clear improvement, no vomiting, but still nauseated.
- (4^B) Very clear improvement, no nausea, but still vomiting.
- (5) Complete improvement, no nausea, no vomiting.

This rating was determined by the patient at the end of days 1 and 8.

c. Adverse reactions:

THC-Eleven patients reported dizziness. Ten (10) experienced being "high". Two (2) patients discontinued the study because of dysphoric reactions. One (1) patient discontinued after one capsule of THC, when she became pale, stuporous, and anxious. It was later determined that this patient had had similar reactions unrelated to THC in the past which might have been

functional. A total of 6/11 patients experienced dysphoric reactions, including fear and anxiety in 5 patients, time distortion in 4 patients, and hallucinations in 3 patients. Nine (9) patients became somnolent, while 3 experienced ataxia, 3 headache, and 3 parasthesia.

Placebo-While receiving placebo, 2/9 patients had headache and 1/9 had difficulty concentrating.

d. Effectiveness:

Efficacy was determined by comparing scores on Days 1 and 8 in the Marinol group to corresponding scores in the Placebo group.

Because there were so few patients in the study, it is impossible to discern if treatment sequence effects occur. For this reason, three analyses were performed. These were

1. Non-parametric Wilcoxon rank sum test of the first period data for the 9 patients who remained in the complete study.
2. Koch's non-parametric Wilcoxon rank sum tests of the crossover data excluding the one patient who received drug in the sequence THC-THC-PBO.
3. An analysis identical to the sponsor's with the exclusion of Patient 4 data.

The first analysis, utilizing only the first period, would be appropriate under the assumption that treatment sequence effects existed, the second under the assumption that they did not. The second result is based on more (about twice as many) observations. The results were as follows:

Statistical Results

	<u>First Period</u>			<u>Crossover</u>		
	<u>Marinol</u>	<u>Pbo</u>	<u>*p-value</u>	<u>Marinol</u>	<u>Pbo</u>	<u>*p-value</u>
Day 1	1.8	1	.08	2	1	.02
Day 8	3.2	1	.01	3.8	1.4	.02
Av day 1,8	2.6	1	.01	3.0	1.1	.02

*2-tail

d. Efficacy:

Because of the large number of dropouts in the MARINOL group from side effects, this crossover design study is difficult to analyze. For this reason, the study was analyzed as a parallel group study, using only the first period data for all patients. When this analysis is performed, two tail p-values calculated for vomiting severity and number of vomiting episodes are .04 and .02 respectively, in favor of MARINOL. A similar analysis of nausea variables resulted in p-values favoring MARINOL over COMPAZINE, but they were not statistically significant.

e. Conclusion:

This study is an adequate and well-controlled study demonstrating the effectiveness of MARINOL as an anti-emetic. This evidence is impressive in that superiority to an active agent in controlling vomiting was demonstrated. While the study is susceptible to the possibility of baseline differences in emetogenic stimuli, particularly since only the first period was analyzed, there is no reason in a randomized trial to believe that any significant bias with regard to this variable occurred. In addition, positive findings in this study speak to the effectiveness of Marinol as a generally effective anti-emetic, as opposed to one useful only against a specific chemotherapeutic agent.

C. Supportive Studies

3. Ungerleider Study.

a. Design:

Two hundred and thirteen (213) patients were randomly assigned to either MARINOL or COMPAZINE in this double-blind crossover study. Patient ages ranged from 18-82, with mean age of 46-48. Drug was given 1 hour before chemotherapy and each 4 hours for a total of four doses. Doses were given at three levels, 7.5 mg, 10 mg, or 12.5 mg according to body surface area. There were 15 cancer types treated with 69 different single or multiple chemotherapy regimens.

Patients were divided into three groups: Single Course-patients who received one day of chemotherapy in each period; Multiple Course-patients who received several days of chemotherapy in each period; One day non-crossover-patients who only received drug in the first period.

b. Efficacy variables:

Seven levels from no nausea (0) to multiple vomiting (6) were determined one hour before chemotherapy and hourly thereafter. Global evaluation of either complete, partial, or poor responder was also recorded. The patients were asked to compare the first with the second drug and to select the preferred drug.

c. Adverse reactions:

Only 15 of 170 patients (9%) experienced a "high" from MARINOL. Other reactions included disorientation (19/170), drowsiness (59/170), dysphoria (26/170), as well as adverse reactions seen in other studies.

d. Efficacy:

When the study is analyzed as a cross-over, no statistically significant differences are found between MARINOL and COMPAZINE in any of the three groups. However, if only the first period of treatment for each group is analyzed, 2-tail p-values are obtained as follows:

Course	p-value
Single	.04
Multiple	.32
One drug	.84
All pts.	.065

e. Conclusion:

When analyzed as above, the overall p-value is marginally significant in favor of MARINOL, with a strongly positive outcome for the subset of patients who received a single course of chemotherapy. When analyzed as a cross-over, the results are consistent with the comparability of MARINOL and COMPAZINE. The data support the conclusion that MARINOL is safe and effective as an anti-emetic in these patients.

4. Frytak Study.

a. Design:

One hundred sixteen (116) patients were randomized to one of three antiemetic treatments, MARINOL, COMPAZINE or placebo in this double-blind parallel-design trial. All patients had unresectable gastrointestinal cancer or were in a

gastrointestinal surgical adjuvant program. All were outpatients and ages ranged from 21-70 with a median age of 61. There were several chemotherapy regimens, all of which consisted of at least 5-fluorouracil for 5 days and Semustine on day 1. Some patients received additional chemotherapy, and therefore the strongest emetic stimulus was on the first day.

Either 15 mgs MARINOL, 10 mgs COMPAZINE or placebo was given as follows:

Day 1 - 2 hours before, then 2 and 8 hours after chemotherapy

Days 2-4 - 1/2 hour before meals 3 times daily

b. Efficacy Variables:

Complete responder - no nausea or vomiting
Partial responder - nausea only
Poor responder - vomiting.

In addition, the occurrence of nausea and/or vomiting was rated.

c. Adverse reactions:

Thirty four of 38 patients on MARINOL had significant side effects. Twenty eight had sedation, 23/38 experienced a "high", 28/38 had coordination difficulties. Less frequent side effects were dizziness and unsteadiness. Twelve (12) patients withdrew from the study due to MARINOL side effects (7 ataxia, 3 hypotension, 2 psychotomimetic effects), one (1) placebo patient withdrew due to fainting and one (1) COMPAZINE patient withdrew due to restlessness.

d. Efficacy:

The response to the three treatments was as follows:

<u>Treatment</u>	<u>Number of Patients</u>	<u>Response to Treatment</u>		
		<u>Complete</u>	<u>Partial</u>	<u>Poor</u>
Placebo	37	7(19%)	6(16%)	24(65%)
COMPAZINE	41	17(41%)	1(2%)	23(57%)
MARINOL	38	16(42%)	2(5%)	20(53%)

This variable was calculated for the first day of treatment only, as this was the day of strongest emetogenic potential. This resulted in a p-value of .05 in favor of MARINOL (over placebo) when groups are classified as complete vs. non-complete

responders. Statistical analysis showed a p-value of .24 on the original, non-contracted data. There was no statistically significant difference between COMPAZINE and MARINOL. In addition, the number of patients who dropped out due to persistent vomiting was significantly less in the MARINOL group compared to either the placebo or COMPAZINE groups.

e. Conclusion:

This study provides some support for the efficacy of MARINOL because the number of patients who had a complete response to MARINOL (ie., no nausea or vomiting), was significantly greater than those who responded completely to placebo but it is weakened by the failure of the uncategorized data to show a significant difference on the original data categorization scale.

The number of patients who dropped out due to persistent vomiting was significantly greater on both placebo and COMPAZINE than MARINOL, a further suggestion of effectiveness.

5. Ekert Study.

a. Design:

This was an open study of eighteen (18) children with ages ranging from 3 to 18 years. Metaclopramide was given at a dose of 5 or 10 mg per $0.7M^2$ of surface area to the first 16 children 2 hours before chemotherapy and 8, 16 and 24 hours after the first dose. Placebo was given at 4 hours. COMPAZINE was given to two (2) children at a dose of 5 mg on the same schedule as metaclopramide, including placebo at the 4-hour interval. MARINOL was given to the same children at another course of chemotherapy. All patients received MARINOL second. The dose of MARINOL was 10 mg/ M^2 with a maximum of 15 mg given 2 hours before chemotherapy, then 4, 8, 16 and 24 hours after the first dose. The children had seven (7) types of cancer and were given 14 different chemotherapy regimens.

b. Efficacy Variables:

The occurrence of nausea and vomiting were each graded as either none, moderate, or severe. In addition, patients were categorized according to overall response similar to previous studies.

c. Adverse reactions:

No patients had a dysphoric reaction and none discontinued the study. The most prevalent reaction on MARINOL was somnolence (13/18) while 2 of 11 experienced a "high." Three children had tachycardia.

d. Efficacy:

While all patients experienced either moderate or severe nausea and vomiting following metaclopramide or COMPAZINE, 9 (50%) experienced complete response after MARINOL. The change in response recorded was as follows:

	<u>Same</u>	<u>Better</u>	<u>Worse</u>	<u>p-value</u>
Nausea	6	11	1	.01
Vomiting	5	12	1	.01

e. Comment:

Several design flaws weaken this study. First, since all patients received MARINOL second, any potential bias due to period or sequence effects cannot be determined. In addition, these patients were chosen to receive MARINOL because they had not had a satisfactory response to standard anti-emetics, so a potential bias against the alternative drugs existed in the population studied.

Despite these shortcomings, however, the study supports the efficacy of MARINOL. The significant number of patients who improved (in addition to the 9/18 who responded completely) is strongly suggestive of an anti-emetic effect. Finally, the fact that these patients were chosen to receive MARINOL on the basis of a previously unsatisfactory response is not a major flaw, as MARINOL will be indicated in just such a refractory population.

6. Laszlo study.

a. Design:

This is an uncontrolled open study of MARINOL in 113 patients who failed to respond to previously administered antiemetics. Ages ranged from 18-72. There was a total of 21 types of cancer treated with 41 different single or combination chemotherapy regimens. The first nine patients received 15 mg/M² of MARINOL while the remaining received 5 mg/M², every 4 hours starting 8-12 hours prior to chemotherapy and continuing for 4 doses afterwards.

b. Efficacy Variables:

As in previous studies, the occurrence of nausea and vomiting were rated independently from none to severe, and an overall response was determined.

c. Adverse reactions:

Five (5) patients were discontinued due to severe dyspnoic reactions; two had been given the initial high dose of 15 mg/M². One hundred (100) of 113 (88%) experienced a "high" and 88% experienced somnolence. Fifty one of 113 (44%) had dry mouth. Other reactions were much less frequent.

d. Efficacy:

The investigator reported the following results for the 108 patients who completed the study:

Complete response	22 (20.4%)
Partial response	57 (52.8%)
No response	29 (26.8%)

e. Conclusion:

This study used essentially historical controls, and even that data was obtained retrospectively, making the interpretation of the results problematic. However, approximately one fifth (1/5) of the patients had a complete response to MARINOL. These patients were only included in this study if they had had a moderate-severe rating on nausea and/or vomiting on previously administered anti-emetics. Therefore, to the extent that response to MARINOL could be considered, in fact, drug related (as opposed to a placebo response or due to a different confounding factor), this result can be considered supportive, albeit weakly, of the efficacy of MARINOL.

D. Remaining Studies

7. Levitt Study.

a. Design:

This parallel group, randomized, double-blind study comparing 5, 10 and 15 mg of MARINOL with 10 mg COMPAZINE, placebo and no treatment. There were 117 patients with ten (10) types of cancer treated with 38 different single or multiple chemotherapy regimens. Ages ranged from 20-79, with a mean age of 57.3. Drug was given 2 hours before chemotherapy and 4, 8 and 12 hours after the first dose.

b. Efficacy variables:

Occurrence, duration and time of onset of both nausea and vomiting were recorded. The investigator also rated the overall response as poor, fair, good or excellent.

c. Adverse reactions:

<u>Reaction</u>	<u>MARINOL</u>	<u>COMPAZINE</u>	<u>Placebo</u>	<u>Control</u>
Drowsiness	73%	67%	77%	61%
Mild depression	23	29	41	9
Severe depression	25	-	-	8
Elated	12	24	14	28

d. Efficacy:

No statistically significant differences were found between any of the treatment groups.

e. Conclusion:

This study is considered negative.

E. Overall Summary Of Safety Data

In controlled clinical trials the most frequently reported adverse reactions were extensions of the pharmacologic activity of MARINOL and principally involved the central nervous system.

In decreasing order of frequency these events were drowsiness, dizziness, muddled thinking and brief impairment of coordination, sensory and perceptual functions.

Easy laughing, elation and heightened awareness, often termed a "high", was observed in 24% of MARINOL patients.

The following side effects were seen in controlled clinical studies in decreasing order of frequency.

FREQUENCY OF ADVERSE EFFECTS
FROM CONTROLLED STUDIES

Body System/ Adverse Reaction	MARINOL (n=317)	Control (n=263)	Placebo (n= 68)
CENTRAL NERVOUS SYSTEM:			
Drowsiness	48	33	49
Dizziness	21	5	1
Muddled Thinking	12	1	1
Perceptual Difficulties	11	1	0
Anxiety	16	3	24
Coordination impairment	9	2	10
Irritability/weird feeling	7	3	0
Depression	7	3	15
Weak, sluggish	6	3	1
Headache	6	4	4
Hallucinations	5	0	0
Memory lapse	5	1	0
Unsteadiness, ataxia	4	1	0
Paranoia	2	0	0
Disorientation, confusion	1	0	2
Depersonalization	2	0	0
AUTONOMIC NERVOUS SYSTEM:			
Dry mouth	3	1	1
Paresthesia	3	0	1
Visual Distortions	3	0	0
CARDIOVASCULAR:			
Tachycardia	1	1	0
Postural hypotension	1	0	0

F. Biopharmaceutics

Due to the severity of the condition to be treated with MARINOL, 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 360 days of the approval of this application, the appropriate bioavailability, bioequivalence, and dose proportionality studies.

VI. Pertinent Advisory Committee Minutes:

The issue of the use of dronabinol (delta-9-THC) as an anti-emetic in patients receiving cancer chemotherapy has been discussed at three separate advisory committee meetings.

1. Oncologic Drugs Advisory Committee: June 26, 1980

At this meeting, the committee decided that delta-9-THC met the criteria for Group C distribution. This is a National Cancer Institute classification that allows wide use of an experimental drug under strict guidelines.

2. Oncologic Drugs Advisory Committee: June 25, 1981

At this meeting, a report on the progress of the program initiated as a result of the previously approved Group C distribution was presented.

3. Drug Abuse Advisory Committee: June 29, 1981

At this meeting, the committee voted to place MARINOL in Schedule II under the Controlled Substances Act if and when the application was approved.

VII. Post-Marketing Surveillance:

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

VIII. Approved Package Insert:

Attached.

FPI

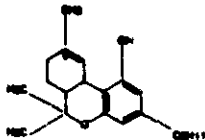


MARINOL® DRONABINOL

CAUTION: Federal law prohibits marketing without prescription.

DESCRIPTION:

MARINOL brand of dronabinol (delta-9-tetrahydrocannabinol, THC) (CAS# 528-11-6) is 7,8,10a-tetrahydro-6,6,9-trimethyl-3-pyridyl (4) dibenzofuran-1-ol is the principal psychoactive substance present in Cannabis sativa L. (marijuana). It has the empirical formula C₂₁H₃₆O₂ with the molecular weight of 314.48. It has the following structural formula:



MARINOL is chemically synthesized and formulated in sesame oil and encapsulated in hard gelatin capsules for oral administration.

CLINICAL PHARMACOLOGY:

Non-therapeutic Effects:

Dronabinol commonly known as delta-9-THC, is one of the major active substances in marijuana. For practical purposes, the non-therapeutic effects of dronabinol may be considered as similar to those of marijuana and other orally active cannabinoids. MARINOL is highly abuseable and can produce both physical and psychological dependence.

Dronabinol has complex effects upon the central nervous system. Subjects using cannabis may experience changes in mood (euphoria, detachment, depression, anxiety, panic, paranoia, etc.), impairment in cognitive performance, and memory, a decreased ability to control drives and impulses, and alterations in the experience of reality (e.g., distortion in the perception of objects and time, loss of time hallucinations, etc.). These latter phenomena appear to be more common when larger doses of dronabinol 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.

Reliable information on the behavioral effects of chronic dronabinol use is not available; however, it has been reported that chronic use of cannabis may be associated with impairments in motivation, attention, judgment, etc. (whether these impairments reflect the underlying character of individuals chronically abusing cannabis or are a result of the use of cannabis is not known).

Dronabinol, used within or slightly above the recommended dose range, has several systemic effects of interest. It characteristically causes an increase in heart rate and conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or lightheadedness upon standing. In one study, a slight but consistent decrease in oral temperature was reported.

The potential of dronabinol to cause tolerance and physical dependence was examined in a 30 day long dose tolerance study. Following thirty days of use, tolerance developed to the cardiovascular and subjective effects of dronabinol administered at doses up to 310 mg/day. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. Fall in supine blood pressure made worse by standing was also observed initially. Within days, however, these effects disappeared, indicating the development of tolerance.

A withdrawal syndrome, consisting of irritability, insomnia, and restlessness, was observed in some subjects within 12 hours following abrupt withdrawal of dronabinol. The syndrome reached its peak intensity at 24 hours when subjects exhibited "hot flashes", sweating, rhinorrhea, loose stools, hiccuping and anorexia. The syndrome was essentially complete within 96 hours.

Electroencephalographic changes recorded following dronabinol discontinuation were consistent with a withdrawal syndrome. While on drug, dronabinol produced a decrease in REM sleep. Following discontinuation, a marked rebound of REM sleep occurred. Several subjects reported impressions of disturbed sleep for several weeks after discontinuing high dose dronabinol. Dronabinol is not an anxiolytic, and does not cause anxiolytic effects upon respiration or fluid use.

Metal Effect and Pharmacokinetics:

Reliable information on the pharmacokinetics of MARINOL is not yet available. The following summary highlights important aspects of the literature concerning the absorption, distribution, metabolism and elimination of dronabinol; however, differences in the preparation, formulation and method of administration make it difficult to extrapolate the information directly to the drug product MARINOL.

Following oral administration, dronabinol has a systemic availability of 10 to 20% relative to an IV dose indicating that the drug undergoes extensive first pass metabolism. Numerous metabolites have been identified, including 11-hydroxy-dronabinol, a brain, which is psychoactive. Dronabinol has a volume of distribution about 100 times as large as the plasma volume.

The maximum plasma concentrations of dronabinol, the 11-hydroxy metabolite, and several other metabolites occur approximately 2 to 3 hours after oral dosing. Biliary excretion is the major route of elimination. Within 72 hours following oral administration, approximately 50% of the dose is recovered in feces, another 10 to 15% is excreted in the urine either unchanged or as a metabolite. Renal clearance in humans is approximately one-tenth of the glomerular filtration rate.

The elimination phase of dronabinol exhibits biphasic kinetics with an initial half-life of about 4 hours and a terminal half-life of 26 to 36 hours. The principal active metabolite, 11-OH-dronabinol, appears in the plasma in roughly the same mg quantities as its parent. The terminal plasma half-life for the 11-OH-dronabinol is approximately 15 to 18 hours. Thus, extended use of MARINOL at the doses recommended in the labeling may cause the accumulation of toxic amounts of dronabinol and its metabolites.

INDICATIONS AND USAGE:

MARINOL is 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 indication is restricted because a substantial proportion of patients treated with MARINOL can be expected to experience disturbing psychotropic reactions not observed with other antiemetic agents. Because of its potential to alter the mental state, MARINOL is intended for use under circumstances that permit close supervision of the patient by a responsible individual.

MARINOL is highly abuseable and controlled under Schedule II of the Controlled Substances Act. Prescriptions of MARINOL should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a 14 day cycle).

Evidence supporting the efficacy of MARINOL in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from a variety of sources. The most persuasive evidence was obtained in patients being treated with MOPP for Hodgkin's and non-Hodgkin's lymphomas. Other evidence supports the conclusion that MARINOL is effective against nausea and vomiting induced by other cancer chemotherapy regimens employed in the treatment of a wide variety of tumor types.

CONTRAINDICATIONS:

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

MARINOL is contraindicated in any patient known to be hypersensitive to either dronabinol or sesame oil.

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 MARINOL. The effects of MARINOL may persist for a variable and unpredictable period of time following its oral administration. Dronabinol is highly lipid soluble and its metabolites may persist in tissues, including plasma, for days. Because of individual variation in response and tolerance to the effects of MARINOL, the physician should determine an initial period of patient supervision required. Patients receiving MARINOL 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 MARINOL for controlled may have serious untoward responses not predicted by prior uneventful exposures. Because a psychotic patient is a potential danger to himself and/or others, any patient who has a psychotic experience with MARINOL 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 MARINOL until he/she has been observed, and the consequences evaluated, by a physician. If the clinical situation warrants, a lower dose of MARINOL 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 MARINOL.

MARINOL should not be taken with alcohol, sedatives, hypnotics, or other psychotropic substances.

PRECAUTIONS:

General:

Because it may cause a general increase in central sympathetic activity, MARINOL should be used with caution in persons with hypertension or heart disease. MARINOL should be used cautiously in manic, depressive, or schizophrenic patients as the symptoms of these disease states may be unmasked by the use of cannabinoids. MARINOL should be used with caution in individuals receiving other psychoactive drugs.

Rev

PhARM

Review and Evaluation of the Pharmacology and Toxicology Data of
NDA 18-651

Sponsor: Unimed Inc.
35 Columbia Road
Somerville, NJ 18876

Drug: Marinol

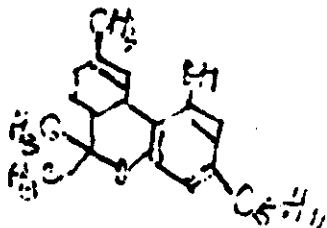
Category: Antiemetic for nausea and vomiting induced by cancer
chemotherapeutic agents

Route: Oral capsule

Formulation: Delta-9-THC in sesame oil

Chemical Name: 3-pentyl-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo
[b,d] pyran-1-ol

Structural Formula: Delta-9-tetrahydrocannabinol (Delta-9-THC)



Related Drugs: The cannabinoids

Related IND: [REDACTED]

I. Acute Studies

1. Acute Toxicity of Delta-9 and Delta-8-THC after Single Oral and Intravenous Doses to Rats, Monkeys and Dogs
2. Toxicity in Rats, Dogs and Monkeys after Acute Administration of Delta-9-THC, Delta-8-THC and Crude Marijuana Extract

II. Subacute Studies

1. Toxicity Observed in Fischer Rats Treated per Os for Five Consecutive Days with Delta-9-THC.
2. Toxicity Observed in Fischer Rats Treated per Os for Five Consecutive Days with Delta-8-THC.
3. Toxicity Observed in Fischer Rats Treated per Os for Five Consecutive Days with Cannabis Extract.
4. Toxicity Observed in Rhesus Monkeys Treated per Os for Seven Consecutive Days with Large Doses of Delta-9- or Delta-8-THC.
5. Toxicity Observed in Fischer Rats Treated for 28 Consecutive Days with Delta-9-THC.
6. Toxicity Observed in Fischer Rats Treated for 28 Consecutive Days with Delta-8-THC.
7. Toxicity Observed in Fischer Rats Treated per Os for 28 Consecutive Days with Crude Marijuana Extract.

III. Chronic Studies

1. Toxicity Observed in Fischer Rats Treated per Os for 119 Consecutive Days with Delta-9-THC.
2. Toxicity Observed in Fischer Rats Treated per Os for 119 Consecutive Days with Delta-8-THC.
3. Toxicological Manifestations in Fischer Rats Treated Orally with Delta-9-THC at Doses Equivalent to American Marijuana and Hashish for 28 Consecutive Days (Interim Report).
4. Toxicological Manifestations in Fischer Rats Treated Orally with Delta-9-THC at Doses Equivalent to American Marijuana and Hashish for 90 Consecutive Days (Interim Report).
5. Toxicological Manifestations in Fischer Rats Treated Orally with Delta-9-THC at Doses Equivalent to American Marijuana and Hashish for 180 Consecutive Days (Final Report).

IV. Reproduction and Hormonal Studies

1. Reproduction Study with Delta-9-THC in Albino Rats (IBT).
2. Teratogenic Study with Delta-9-THC in Albino Rats (IBT).

3. Perinatal and Lactation Performance Study with Delta-9-THC in Albino Rats (IBT)
4. Serum Hormone Levels and 30-Day Recovery of Fischer Rats Treated Orally with Delta-9-THC for 180 Consecutive Days (MRI)
5. Serum Hormone Levels in pregnant Fischer Rats Treated Orally with Delta-9-THC (Status Report, MRI).
6. Serum Hormone Levels in Non-Pregnant and pregnant Fischer Rats Treated Orally with Delta-9-THC (Final Report).
7. The Effects of Delta-9-THC on Pregnancy and Fetal Mortality in Mice and Rats (MRI).
8. The Effects of Delta-9-THC in Pregnancy and Fetal Mortality in Rats Established Pregnant by Laparotomy (MRI).
9. Effect of Long Term Oral Treatment of Delta-9-THC on the Male Rat Reproductive Endocrine System.
10. Mouse Teratology Study with Delta-9-THC Administered Orally During Days 6-15 of Gestation (Interim, MRI).
11. Mouse Teratology Study with Delta-9-THC Administered Orally During Days 6-15 of Gestation (Final Report, MRI)
12. The Effect of Intra-gastric Administration of Delta-9-THC on the Growth and Development of Fetal Mice of the A/J Strain.
13. Teratogenic Study with Delta-9-THC in Albino Rabbits.

V. Cytogenetic Studies

1. Acute Cytogenetic Effects of Single Oral Doses of Delta-9-THC on Female Sprague Dawley Rats at Intervals of 6, 12, 18, 24, 48, and 96 hrs.

NDA 18-651 (Marinol)
Acute Toxicity

Acute Toxicity of Delta-9- and Delta-8-THC After Single Oral and Intravenous Doses to Rats, Monkeys and Dogs. (Contract No. HSM-42-70-95, 9/17/70)

Toxicity in Rats, Dogs and Monkeys After Acute Administration of Delta-9-THC, Delta-8-THC and Crude Marijuana Extract (Contract No. HBM-42-71-79, 8/17/70-3/1/71).

I. Rats

Site: MRI, Worcester, Massachusetts 01608

Species/Strain: Wistar Lewis rats

- a. Route: p.o.
of rats/level: 3-5 rats/sex/level, 10 rats/sex for vehicle control
Dose Levels: Delta-9-THC - 0, 225, 450, 675, 900, 1350, and 1800 mg/kg

Vehicle: [REDACTED]
Treat Vol: 1.0-3.0 ml/100 gm B.W.)

- b. Route: I.V.
of rats/treatment (Vehicle only): 4-5/sex
Vehicle: [REDACTED]
Injection Vol: 0.3 ml/100 gm B.W.

Species/Strain: Fischer rats

- a. Route: p.o.
of rats/level: 10-15 rats/sex/level
Dose Levels: Delta-9- and Delta-8-THC - 0, 225, 450, 900, 1800, 2700 and 3600 mg/kg
CME----0, 625, 1250, 2500, 5000 and 7500 mg/kg

Vehicle: [REDACTED]
Treat. Vol: 1.0-3.0 ml/100 gm B.W.

- b. Route: i.v.
of rats/level: 5-10 rats/sex/level
Dose Levels: Delta-9-THC -- 0, 10, 15 and 20 mg/kg
Delta-8-THC -- 20, 25, 30, 40, 60 and 80 mg/kg
Vehicle: [REDACTED]
Injection Vol: 0.2-0.3 ml/100 gm B.W.

Results:

1. Median Lethal Dose Levels for Delta-9- and Delta-8-THC and CNE

<u>Strain</u>	<u>Compound</u>	<u>Route</u>	<u>Purity</u>	<u>Vehicle</u>	<u>Sex</u>	<u>LD50 in mg/kg</u> <u>(95% CL)</u>
Fischer	Delta-9-THC	p.o.	96%	[REDACTED]	M	1015 (720-1320)
			90%	[REDACTED]	F	800 (530-1010)
	i.v.	[REDACTED]	M	1910 (1390-2680)		
		[REDACTED]	F	1040 (820-1320)		
		[REDACTED]	M&F	15-20		
		[REDACTED]				
Delta-8-THC	p.o.	99%	[REDACTED]	M	1980 (1580-2470)	
	i.v.	[REDACTED]	F	860 (680-1090)		
				M&F	20-25	
CNE	p.o.	a	[REDACTED]	M	3300 (2480-4390)	
				F	1380 (950-2020)	
Wistar-Lewis	Delta-9-THC	p.o.	90%	[REDACTED]	M	1160 (850-1582)
					F	860 (640-1160)

A. CNE contained: [REDACTED]

I.V. route produced vertical dose-response curve for both Delta-9- and Delta-8-THC, i.e., no death at 15 mg/kg (Delta-9-) and 20 mg/kg (Delta-8-) and 100% mortality at 20 mg/kg (Delta-9) and 25 mg/kg (Delta-8-).

95% of deaths treated orally succumbed 36-72 hrs post treatment while all I.V. treated, deceased deaths died in 6 minutes post treatment.

2. Signs of toxicity were similar for all three compounds. These included inactivity, wide stance, hypersensitivity to touch, backward circling, hyperactivity, ataxia, catatonia, severe hypothermia (30-60% decrease) rapid weight loss (15-25%, reversible), decreased resp. rate and generalized body twitches (popcorn convulsions). I.V. produced similar behavioral changes except that toxicity progressed more rapidly, popcorn convulsions occurred more frequently, and no hypothermia and inanition were observed. Deaths were due to respiratory arrest.

In general, as dose increased, onset of initial behavioral changes decreased, duration of effects increased and the developmental sequence of behavioral observations extended.

3. Compound potency (p.o.) were: Delta-9-THC Delta-8-THC CME.
4. For the two strains studied, female rats were significantly more sensitive to all three compounds than male rats.
5. Strain difference in Delta-9-THC susceptibility was also observed. Wistar-Lewis rats were found to be more susceptible to Delta-9-THC than Fischer rats.
6. All vehicles employed were tolerated except the following two which were not tolerated in Wistar-Lewis rats:
 - a. [REDACTED] administered orally for 5 days produced inactivity, dehydration and mottled fur in all rats. One male died on Day 3 of treatment. Survivors were normal 7 days after cessation of treatment. This vehicle was not used in subsequent experiments.
 - b. [REDACTED] 0.05 ml/100 gm produced ataxia and prostration in 2/6 rats.

II. Monkeys

Species/Strain: Rhesus monkeys

- a. Route: p.o.
of monkeys/level: 1 monkey/sex/level
Dose levels: Delta-9-THC -- 0, 131.3, 262.5, 525, 736*, 1050 and 3150 mg/kg; Delta-8-THC -- 131.3, 262.5, 525, and 1050 mg/kg; CME--5000 mg/kg
Vehicle: [REDACTED]
Treat Vol: 2 ml/kg for Delta-9-and Delta-8-THC, 7.7 ml/kg for CME
- b. Route: i.v.
of animals/level: 1 monkey/sex/level
Dose Levels: Delta-9-THC - 0, 3.9, 15.6, 62.5*, 525, and 1050 mg/kg
Vehicle: [REDACTED]
Treat. Vol: 0.5 ml/kg except 62.5 mg/kg (solution conc. of 500 ng/ml) and 1050 mg/kg at which 0.12 ml/kg and 1 ml/kg respectively were used.
*Two solution concentrations were employed, i.e. 125 x 500 ng/ml

1. Mortalities of Monkeys Treated with Delta-9-THC, i.v.

Dose (mg/kg)	0	3.9	15.6	62.5	525	1050
Mortality	0/3**	0/2	0/2 ⁺	2/4*	3/3	1/1

[REDACTED]

+The two monkeys survived only after artificial respiration

*2 monkeys died at solution concentration of 125 ng/ml while the other two survived at 500 ng/ml

[REDACTED]

Monkeys, acute, p.o.

1. Delta-9-THC

Dose (mg/kg)	<u>0</u>	<u>131.3</u>	<u>262.5</u>	<u>525</u>	<u>736</u>	<u>1050</u>	<u>3150</u>
Mortality	0/2	0/2	0/2	0/2	0/1	0/2	0/2

[REDACTED]

Vehicle: [REDACTED]

2. Delta-8-THC

Dose	<u>0</u>	<u>131.3</u>	<u>262.5</u>	<u>525</u>	<u>1050</u>
Mortality	0/2	0/2	0/2	0/2	0/2

Vehicle: [REDACTED]

3. CME

Dose	<u>0</u>	<u>5000</u>
Mortality	0/2	0/2

Vehicle: [REDACTED]

Doses of 525 and 1050 mg/kg killed every monkey tested. At 62.5 mg/kg, mortality appeared to be solution concentration dependent, i.e., 2/2 mortality at 125 ng/ml and 0/2 at 500 ng/ml. Since 15.6 mg/kg was survived by 2/2 monkeys only because of artificial

respiration, the maximum non-lethal single i.v. dose to monkeys was 3.9 mg/kg. All deaths occurred within 5 minutes to 40 hrs and were due to respiratory failure in all cases. Gross necropsy of all animals that died revealed severe pulmonary hemorrhage and edema. No mortalities occurred in monkeys treated p.o. with 131.3 to 3150 mg/kg Delta-9-THC, 131.3 to 1050 mg/kg Delta-8-THC or with 5000 mg/kg CME, p.o.

2. Behavioral changes following the administration of three compounds were similar in all monkeys. Administered orally, the three compounds produced initial hyperactivity and hypersensitivity which progressed to drowsiness and a characteristic huddled posture. In this position the animals reacted slowly to external stimuli. Potency of the three compounds was similar to that seen in the rat study, i.e. Delta-9-THC : Delta-8-THC : CME (5 gm/kg CME was approximately equi-potent to 1 gm/kg Delta-9-THC) Recovery of the monkey was complete in 2-4 days.

Monkeys treated intravenously exhibited pharmacotoxic signs similar to that of the oral route except that the onset was more rapid and the intensity was more severe. Additional signs included aggressiveness, inactivity, sedation, prostration, convulsion, anesthesia and deaths.

3. Clinical changes (emesis, anorexia, hypothermia, and facial pallor) observed in monkeys treated p.o. or i.v. with Delta-9-THC or p.o. with Delta-8-THC or CME were of low incidence and minor significance.
4. Vehicle Toxicity

a. Intravenous Route

1. [REDACTED] - 0.20 - 0.45 ml/kg produced no pharmacotoxic signs
- - 0.7 mg/kg showed facial pallor incoordination, drowsiness and ataxia
2. [REDACTED] 2.0 ml/kg produced facial congestion and erythmia, was discontinued due to severe reactions seen in dogs.
3. [REDACTED] 0.3 ml/kg was well tolerated
- - 1.0 ml/kg produced prostration, emesis and anorexia
4. [REDACTED]

b. Oral Route

1. [REDACTED] -- 1.0 ml/kg was well tolerated
-- 2.0 ml/kg produced hyperactivity followed by drowsiness
2. [REDACTED] -- 3.33 ml/kg tolerated
3. [REDACTED] -- 3.6 ml/kg, tolerated
4. [REDACTED] -- 3.2 ml/kg tolerated

III. Dogs

Species/Strain: beagle dogs

a. Route: p.o.

of dog(s)/level: 1-2 dogs/sex/level

Dose Levels:

Delta-9-THC - 0, 65.6, 131.3, 262.5, 525*, 1050 and 3000 mg/kg

Delta-8-THC - 65.6, 131.3, 262.5, and 525 mg/kg

CME - 5000 mg/kg (only one male dog was used and treatment volume was 7.46 ml/kg)

Vehicle: [REDACTED]

Treatment Vol: - ml/kg except Delta-9-THC at 525 and 1050 mg/kg in which 0.5 ml and 3 ml/kg were administered.

*Two vehicles were used, i.e. [REDACTED]

b. Route: i.v.

of animal(s)/level: 1 dog/sex/dose

Dose Levels:

Delta-9-THC -- 0, 3.9, 25, 100 and 210 mg/kg

Vehicle: [REDACTED]

Treatment Vol: 0.2 ml/kg

Results:

1. Mortalities in beagle dogs treated i.v. with Delta-9-THC occurred at 100 mg/kg (1/2) and 210 mg/kg (2/2). One dog treated p.o. with 525 mg/kg Delta-9-THC and one dog treated p.o. with 5000 mg/kg CME died after aspiration of the compound. All other dogs survived and treatment with 65.6-3000 mg/kg Delta-9-THC or 65.6-525 mg/kg Delta-8-THC. Deceased dogs showed extensive pulmonary hemorrhages and edema.

Mortality

i.v.

1. Delta-9-THC

Dose (mg/kg)	0	3.9	25	100	210
Mortality	0/2	0/2	0/2	1/2	2/2

Vehicle: [REDACTED]

p.o.

1. Delta-9-THC

Dose (mg/kg)	0	65.6	131.3	262.5	525	1050	3000
Mortality	0/2	0/2	0/2	0/2	1*/4	0/1	0/1

Vehicle: [REDACTED]
 *: died after aspiration of the compound

2. Delta-8-THC

Dose (mg/kg)	0	65.5	131.3	262.5	525
Mortality	0/2	0/2	0/2	0/2	0/2

Vehicle: [REDACTED]

3. CME

Dose (mg/kg)	0	5000 mg/kg
Mortality	0/1	1*/1

Vehicle: [REDACTED]
 *died after aspiration of the compound

2. Pharmacotoxic signs in dogs treated i.v. with Delta-9-THC included dose related ataxia, loss of equilibrium, intermittent prostration, salivation, emesis, dyspnea or hypopnea, anesthesia and severe hypothermia. Additional signs included muscle twitches, muscle spasms and clonic and tonic convulsions

with opisthotonus. Animals treated orally showed the same toxic changes except that these signs were not dose related and toxicity was generally less severe.

3. The pharmacotoxic signs of dogs treated p.o. with Delta-8-THC were similar to those seen with Delta-9-THC but were less severe, occurred more slowly and had a shorter duration of action.

4. Vehicle toxicity

A. Intravenous Route

1. [REDACTED] not tolerated, 1 ml/kg of as low as [REDACTED] produced ataxia and erythmia in dogs
2. [REDACTED] -- 0.2 ml/kg well tolerated except in one dog
3. [REDACTED] -- 0.2 ml/kg well tolerated

B. Oral Route

1. [REDACTED] -- 1.0 ml/kg, tolerated
2. [REDACTED] -- 0.75 ml/kg, tolerated
3. [REDACTED] -- 0.5 ml/kg, not well tolerated, produced ataxia and prostration

Subacute Toxicity

Toxicity Observed in Fischer Rats Treated per Os for Five Consecutive Days with Delta-9-tetrahydrocannabinol

Site: MRI, Worcester, MA 01608

Study # & Date: Contract HSM-42-70-95, 12/18/1970

Species/Strain: Fischer Rats

of rats/level: 10 rats/sex/level

Dose levels: 0, 62.5, 125, 250, 500 and 1000 mg/kg

Route: gavage (sesame oil)

Treatment vol: 0.5 ml/100 gm B.W. (except the 1000 mg/kg group which received 1.0 ml/100 gm)

Duration: 5 days

Parameters Studied:

Body weights, rectal temperature and respiration rates were measured on days 1 through 8. Behavioral observations were made at 1, 2, 5 and 24 hrs after each treatment and daily on days 6 through 12. Urinalysis hematologic and blood chemical determinations, gross and pathological changes and organ weight changes were done at the end of the study.

Results:

1. Pharmacotoxic signs include: slow movement, inactivity, lacrimation, sensitivity to touch, mottled fur, dehydration, diarrhea, hypopnea and hypothermia of dose related incidence.
2. All 1000 mg/kg rats died during treatment. Among the 500 mg/kg group two males and four females died on the second day of treatment. All other treated rats survived the study.

Mortality of Fischer Rats Treated With Delta-9-THC, p.o. For Five Days

Dose (mg/kg)	0	62.5	125	250	500	1000
Mortality	1*/20	0/20	0/20	0/20	6/20 [2M + 4F]	20**/20

*One male died due to colon puncture during rectal temperature measurement.
 **One female died on Day 1 due to gavage intubation procedure.

3. The 500 and 1000 mg/kg rats showed bone marrow hypocellularity and germinal center atrophy in the spleen upon histopathological examinations. Bone marrow changes included a decrease in megakaryocytes and myeloid cells with fatty infiltration while splenic changes consisted of a decreased number and cellularity of germinal centers. The 1000 mg/kg group also exhibited testicular changes seen as hemorrhage, spermatozoa necrosis, and hyperemia.

Histopathology

	<u>0</u>		<u>500 mg/kg</u>		<u>1000 mg/kg</u>	
	Severity*	% response	Severity*	% response	Severity*	% response
		<u>M</u> <u>F</u>		<u>M</u> <u>F</u>		<u>M</u> <u>F</u>
Bone marrow: hypocellularity			++	90 100	++	80 100
Spleen: germinal center atrophy			+	20 40	++	70 100
Testes: hemorrhage					+++	10
spermatozoa necrosis					++	10
hyperemia					+	10
Lung: congestion			+	10 20	+	10

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe,
 No entry = no visible lesion

- a. Number of animals subjected to histopathological examination not specified.

4. The 500 and 1000 mg/kg groups showed reduced weight gain. Changes in organ weights were also observed in these two groups: decreased spleen weights (both absolute and relative) for both sexes at 1000 mg/kg and for females at 500 mg/kg; increased adrenal weights (both absolute and relative) for males at 500 and 1000 mg/kg; and increased liver weights (absolute and relative) for females at 1000 mg/kg.
5. Hematological findings revealed that leukopenia was associated with the treated groups although the incidence was generally low in all groups. Several rats exhibited marked to severe leukopenia with neutrophils and lymphocytes equally affected.
6. The only consistent blood chemical changes observed in tested rats were a moderately elevated SGOT level and the incidence was low in all groups. Urinalysis revealed no apparent adverse drug related changes.
7. Rats receiving 62.5, 125, and 250 mg/kg showed tolerance; the degree of tolerance was inversely related to dose.

Toxicity Observed in Fischer Rats Treated per Os for Five Consecutive Days with Delta-8-Tetrahydrocannabinol

Site: MRI, Worcester, MA 01608

Study # & Date: Contract HSM-42-70-95, 1/29/71

Species/strain: Fischer rats

of rats/level: 10/sex/level

Dose levels: 0, 62.5, 125, 250, 500 and 1000 mg/kg

Route: gavage (sesame oil)

Treatment Vol: 0.5 ml/100 gm B.W. (except the 1000 mg/kg group which received:
1.0 ml/120 gm)

Duration: 5 days

Observation parameters: Same as Five-Day Study with Delta-9-THC in Fischer rats

Results:

1. Pharmacotoxic signs observed were identical to those seen in previous studies with Delta-9-THC. Treated rats showed weight loss, hypothermia and hypopnea.
2. All but one of the rats receiving 1000 mg/kg succumbed. Four of the 20 rats receiving 500 mg/kg also died. Deaths resulted from generalized depressions as indicated by ataxia, hypothermia, and hypopnea.

Mortality of Fischer Rats Treated With Delta-8-THC, p.o. for Five Days

Dose (mg/kg)	0	62.5	125	250	500	1000
Mortality	0/20	0/20	0/20	0/20	4/20 [1 M + 3 F]	19/20 [9 M + 10F]

3. Histopathology showed moderate to marked hypocellularity of bone marrow and spleen at 500 and 1000 mg/kg, moderate degeneration of seminiferous tubules, marked necrosis and mineralization in the adrenal cortex and marked vacuolization of the parathyroid gland at 1000 mg/kg.

Histopathology

	<u>0</u>		<u>500 mg/kg</u>		<u>1000 mg/kg</u>			
	Severity*	% response	Severity*	% response	Severity*	% response		
		<u>M</u>		<u>F</u>		<u>M</u>	<u>F</u>	<u>M</u>
Bone marrow, hypocellularity			+	60	70	++	50	80
Spleen germinal center atrophy			+	80	40	++	40	90
Testes, seminiferous tubule degeneration			+	50				
Adrenal, necrosis & mineralization			++	20	10			
vacuolization			++	40	20			
parathyroid, vacuolization			++	30				
Lung, congestion			+	10	10	++	10	20

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe. No entry = no visible lesion

a. Number of animals subjected to histopathological examination not specified.

4. Organ weight changes were similar for rats treated with either Delta-9 or Delta-8-THC, i.e. general pattern of decreasing spleen weights and increasing adrenal and liver weights.
5. Hematology and blood chemistry measurements revealed a non dose-related leukopenia and elevated SGOT in rats treated with Delta-8-THC. These findings were similar to that of Delta-9-THC.
6. Tolerance inversely related to dose was seen by the third day of treatment.
7. Urinalysis was unremarkable.
8. Comparison of Delta-9- and Delta-8-THC subacute effects revealed that the time of onset for clinical changes were identical for the two compounds, but the overall duration of effects was slightly increased and the incidence of response was slightly decreased in rats treated with Delta-8-THC.

Toxicity Observed in Fischer Rats Per Os Treated for Five
Consecutive Days with Cannabis Extracts

Site: MRI, Worcester, MA 01608

Study # and Date: MRI-MH05-71-15, 11/1/70 - 2/10/71; Contract HSM-42-70-95

Species/Strain: Fischer rats

of rats/level: 10/sex/level

Dose Levels: 0, 187.5, 375, 750, 1500 and 3000 mg/kg

Route: Oral (sesame oil)

Treatment Vol: 1 ml/100 gm B.W.

Duration: 5 days

Observation parameters: Same as five day study with Delta-9 and Delta-8-THC in Fischer rats

Results:

1. Toxic signs included inactivity characterized by slow movements and wide stance, tendency to grasp the cage floor firmly or curl into a ball when handled, pallor, lacrimation, diarrhea, dehydration, hypopnea and hypothermia.
2. Tolerance development was inversely related to dose and was manifested by increased rate of recovery or decreased severity of pharmacotoxic signs.
3. All rats treated with 3000 mg/kg died; 10/20 of the 1500 mg/kg group succumbed. The other treated rats as well as the controls survived the experiment. Similar to Delta-9 and Delta-8-THC, deaths resulted from central depression as manifested by inactivity, hypothermia and hypopnea.

Mortality of Fischer Pats Treated With CME p.o. for Five Days

Dose (mg/kg)	0	187.5	375	750	1500	3000
Mortality	0/20	0/20	0/20	0/20	10/20	20/20
					[4 M + 6 F]	

4. Histopathology revealed hypocellularity of spleen and bone marrow, moderate degeneration of seminiferous tubules and adrenal cortex changes in the 750 and 1500 mg/kg groups.

Histopathology

	<u>0</u>		<u>750 mg/kg</u>		<u>1000 mg/kg</u>			
	Severity*	% response	Severity*	% response	Severity*	% response		
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>		
Bone marrow, hypocell. & fat replacement			+	80	80	++	100	90
Spleen, hypocellularity			+	30	50	++	70	90
Lung, congestion			+	10	10	++		10
Testes, seminiferous tubule degeneration	+	20	+	60		+	60	
Adrenal, cortex congestion						+		30
cortex hemorrhage	+++	7	+	20	10	+		20
vacuolization	+	7	+	10	20			

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe, No entry = no visible lesion

a. Number of animals subjected to histopathological examination not specified.

5. Treated rats showed weight loss. The effect was most marked at 375 mg/kg and up and dose related in males. Organ weight changes observed were similar to that of Delta-9 and Delta-8-THC, i.e., increase in adrenal weights, decrease in spleen weights. Also observed were decreases in testes, prostate and uterus weights.
6. Hematological and blood chemical changes included non-dose-related leukopenia, lymphopenia, elevated SGOT and elevated SGPT.

7. Basically, toxic changes observed in rats treated with cannabis extracts coincided with changes observed in rats treated the Delta-9- or Delta-8-THC. The time of onset for clinical changes was identical for the three compounds; the overall duration of effects was identical in rats treated with cannabis extract or Delta-8-THC, but Delta-9-THC treatment slightly extended the duration of individual effects. The severity or incidence of response in rats treated with cannabis extract was slightly less than observed for Delta-8-THC, and much less than observed for Delta-9-THC.
8. Daily administration of Cannabis Extract 187.5 to 750 ng/kg appeared to be well tolerated in Fischer rats.

Toxicity Observed in Rhesus Monkeys Treated Per Os for Seven Consecutive Days with Large Doses of Delta-9- or Delta-8 THC

Site: MRI, Worcester, Massachusetts 01608

Study # & Date: MRI-USGT-71-03, 10/21/70 - 1/12/71

Contract No. HSI-42-70-95

Species/Strain: Rhesus Monkeys

of monkey/sex: 1 monkey/sex.

Dose Schedule: The monkeys were treated with Delta-9 or Delta-8 THC at doses of 1.0 gm/kg/day for two days, 2.0 gm/kg/day for two days and 5.0 gm/kg/day for three days, or with vehicle (corresponding volume administered were 0.2, 0.4 & 1.0 ml/kg/day).

Solution concentration: [REDACTED]

Route: p.o. [REDACTED]

Duration: 7 days

Observation parameters:

The animals were observed at 1, 3, 6, and approximately 24 hrs. after each treatment. Body weights and rectal temperatures were measured prior to each treatment, rectal temperature three hours post treatment each day; serum, urine and feces were collected 24 hrs after the last administration of each dosage (i.e. on days 3, 5 and 8) for determination of THC concentrations. Hematology and blood chemistry were done prior to treatment and on days 8 & 15 post treatment. Autopsy was done on day 8 (female monkeys) and day 15 (male monkeys) for histopathological evaluation and for determination of the total nucleated cell counts of the bone marrow (TNC).

Results:

1. All monkeys survived in good general condition. Treated monkeys (both Delta-9- & Delta-8) showed similar behavioral changes to that observed after single oral treatment which included huddled posture, lethargy, hyper-reactivity to stimuli, occasional decrease in reactivity to painful stimuli, slow movements and changes in attitude. Tolerance was observed approximately on day 5 and was reflected by faster recovery from depression, decreased severity and signs, and an absence of further toxicity as the dose was raised. Additional signs observed included temporary constipation, persistent anorexia, hypothermia and body weight loss.
2. Treated monkeys showed hypocellularity of the bone marrow which was reflected in a consistent decrease in total nucleated cell counts (TNC).

Bone Marrow Total Nucleated Cell Counts (TNC)*

	<u>Vehicle Control</u>	<u>Delta-9-THC</u>	<u>Delta-8-THC</u>
		1.0 gm/kg for 2 days 2.0 gm/kg for 2 days 5.0 gm/kg for 3 days	1.0 gm/kg for 2 days, 2.0 gm/kg for 2 days, 5.0 gm/kg for 3 days.
Male	2.02	1.85	1.75
Female	3.35	1.12	1.46

* TNC/mg bone marrow

3. Gross and histopathology, hematology and blood chemistry revealed no apparent adverse drug related changes. Also organ weights were unremarkable.
4. Serum THC concentration measurements showed a consistent increase in drug levels from 1.0 to 2.0 gm/kg/day but no further increase in serum levels were observed after 5.0 gm/kg/day indicating poor absorption of Delta-9- & Delta-8-THC from the G.I. tract.
5. Vehicle control animals were unaffected by treatments with 0.2 & 0.4 ml/kg ~~absolute EtOH~~, but 1.0 ml/kg administered the last three treatment days produced mild to moderate huddled posture, drowsiness, and reduced motor activity.

Toxicity Observed in Fischer Rats Treated for
28 Consecutive Days with Delta-9-THC

Site: MRI, Worcester, Mass. 01608
Study # & Date: MRI-MH-06-71-16, 12/16/70 - 1/20/71
Contract No. HSI1-42-70-95
Species/strain: Fischer rats
of rats/level: 20/sex/level for 0, 50, & 250 mg/kg;
30/sex/level for 400 & 500 mg/kg
Dose Levels: 0, 50, 250, 400, & 500 mg/kg
Treatment volume: 0.5 ml/100 gm B.W.
Route: gavage (sesame oil)
Duration: 28 days

Observation parameters:

Body weights were recorded weekly while rectal temperatures and respiratory rates were measured 5 hrs. post treatment on days 1 & 7. Behavioral and clinical observations were made 5 hrs. post treatment on days 1, 7, 14, 21 and 28. For 24 hr urine collection 5 male and 5 female rats per dose level were placed 2 to 3 per metabolism cage on day 28 with food and water withheld. Hematological and blood chemical analyses, and gross and pathological evaluations were done at the end of the study (Day 29).

Results:

1. Treated rats exhibited a bimodal pattern of toxicity. During the first 7 to 10 days of treatment, the spectrum and severity of toxicity observed were essentially the same as previously reported for rats treated with single or five consecutive days of Delta-9-THC, i.e., signs of general CNS depression as manifested by inactivity, slow movements, wide stance, constipation, weight loss, hypothermia and hypopnea. Tolerance developed to these depressant effects but the degree of tolerance varied for individual parameters and was inversely related to the dose. As tolerance developed, treated rats exhibited progressively more hyperactivity -- the second phase of toxicity. Enhanced activity was reflected by increased curiosity movements, increased grooming movements and an increased rate of generalized motor activity. During this second phase, a number of treated rats exhibited severe wounds that resulted from fighting. The incidence of this effect was also inversely related to dose and correlated with the hyperactivity observed. Tolerance to hyperactivity was not seen. A low incidence of tremors and chronic convulsions was also observed in rats treated with 250 or 400 mg/kg of Delta-9-THC.

- Mortality was dose related among the 400 and 500 mg/kg rats, i.e. 15/60 died at 400 mg/kg and 50/60 at 500 mg/kg.

Mortality of Fischer Rats Treated With Delta-9-THC,
p.o. for 28 Days

Dose (mg/kg)	0	50	250	400	500
Mortality	0/40	0/40	0/40	15/16 [7 M + 8 F]	50/60 [21 M + 29F]

- During the first week of treatment all treated groups lost weight. At termination, the 50, 250, and 400 mg/kg rats showed reduced weight gain while the surviving 500 mg/kg rats showed weight loss. Food consumption and water consumption measured only on Day 25-28 were not adversely affected by drug treatment.
- Histopathology revealed spleen and bone marrow hypocellularity and vacuolization in the adrenal cortex among 250 and 400 mg/kg rats. Postmortem changes precluded histopathologic evaluation of the surviving 500 mg/kg rats.

	Histopathology							
	0		250 mg/kg				400 mg/kg	
	Severity*	% response	Severity*	% response	Severity*	% response	Severity*	% response
	<u>5</u>	<u>5</u>		<u>6</u>	<u>5</u>		<u>5</u>	<u>5</u>
	<u>M</u>	<u>F</u>		<u>M</u>	<u>F</u>		<u>M</u>	<u>F</u>
Bone marrow, hypocell. & fat replacement	+	20	+	67	60	+	80	60
Spleen: hypocellularity			+		20	+	40	40
Adrenal, vacuolization			+	83	80	+	60	80

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe, No entry = no visible lesion

a. Pathological interpretation of the 500 mg/kg was obscured by post mortem degeneration.

Total Nucleated Cell Counts (TNC)*

	<u>Vehicle</u>	<u>400 ng/kg</u>
	mean $\pm$ S.E.	mean $\pm$ S.E.
M	18.32 $\pm$ 3.34	13.15 $\pm$ 1.53
F	17.70 $\pm$ 1.72	12.67 $\pm$ 3.38

*TNC in 10^6 cells/mg bone marrow, N = 5/sex/group.

- *5. All organ weights were decreased in a dose-related fashion but adrenal glands, which increased in size. Prostate, uterus, and pituitary were most severely affected. The organ weight changes reflected reduced weight gain and/or weight loss.
6. A dose-related loss of abdominal fat and a 10 to 15% decrease in exanguinable blood were also obtained in the treated rats.
7. Hematology and urinalysis revealed no apparent drug related changes.

Toxicity Observed in Fischer Rats Treated for
28 Consecutive Days with Delta-8-Tetrahydrocannabinol

Site: MRI, Worcester, MA 01608
 Study # and Date: MRI-MH08-71-18, 12/23/70-1/27/71
 Contract No HSI-42-70-95
 Species/Strain: Fischer Rats
 # of Rats/Level: 40/sex for control, 20/sex for 50 and 250 ng/kg and 30/sex for 400 and 500 ng/kg
 Dose Levels: 0, 50, 250, 400 and 500 ng/kg
 Treatment Vol: 0.5 ml/100 gm B.W.
 Route: gavage (sesame oil)
 Duration: 28 days
 Observation parameters: same as Study #MRI-MH06-71-16 (12/16/70-1/20/71), i.e. 28 consecutive days with Delta-9-THC

Results:

1. Pharmacotoxic signs of dose related severity included inactivity characterized by slow movement and wide stance, grasping the cage floor or curling into a ball when handled, pallor, diarrhea, hypopnea and hypothermia. Tolerance inversely related to dose was seen on the third day of treatment. This was followed by progressive hyperactivity characterized by increased exploratory movements, grooming movements and

general increased activity. Rats treated with 50, 400 and 500 mg/kg exhibited fighting as evidenced by the number of bitten rats. These lesions were initially confined to the tails which were ultimately completely devoured. The next site of attack was the forelimbs which were totally absent in some rats. These animals also were very irritable when handled. Isolation of the fighting rats halted development of additional lesions indicating that these were due to fighting and not to autocannibalism.

2. Mortality was dose related, i.e, 11/60 at 400 mg/kg and 23/60 at 500 mg/kg.

Mortality of Fischer Rats Treated With Delta-8-THC,
p.o. for 28 Days

Dose (mg/kg)	0	50	250	400	500
Mortality	0/80	0/40	0/40	11/60 [7 M + 4 F]	23/60 [3 M + 20 F]

3. Treated rats showed weight loss during the first week of treatment but this was no longer seen on Day 9. At termination the treated rats showed reduced weight gain. Food and water consumption recorded from Day 15-28 were generally within normal limits, or were slightly increased.
4. Histopathology revealed hypocellularity of the bone marrow and spleen, vacuolization of the adrenal cortex and pulmonary congestion. A dose related loss of abdominal fat and a 10-15% decrease in exanguinable blood were also observed.

Histopathology

	<u>0</u>		<u>250 mg/kg</u>		<u>400 mg/kg</u>		<u>500 mg/kg</u>	
	Severity* H	Response F	Severity* M	Response F	Severity* M	Response F	Severity* M	Response F
Bone marrow, eryloid decrease megakaryocyte decrease	+	20			+	60		
fatty deposition	+	20	+	20	+	60	+	20
Spleen, lymphocyte decrease			+	40	+	40		
Adrenal, cortex vacuolization			+	80	+	60	+	60
neutillar congestion			+	20	+	20	++	40
Lung, congestion							+	60

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe,
No entry = no visible lesion

	<u>Total Nucleated Cell Counts (TNC)*</u>				
	<u>Control</u>	<u>50 mg/kg</u>	<u>250 mg/kg</u>	<u>400 mg/kg</u>	<u>500 mg/kg</u>
M	18.32 ± 3.34	28.87 ± 3.0	18.74 ± 2.8	18.01 ± 2.5	14.31 ± 1.2
F	17.70 ± 1.72	20.32 ± 4.2	29.30 ± 7.5	19.71 ± 1.21 (N = 4)	14.31 ± 1.2 (N = 4)

*TNC in 10^6 cells/mg bone marrow, N = 5/sex/group except where indicated.

5. Testicular changes observed in the Five Day Study were not observed in the current study, therefore, appeared reversible upon continuation of treatment.
6. Prostate, uterus, pituitary and spleen relative organ weights were decreased but adrenal glands increased in size.
7. Hematological findings revealed that increased coagulation time occurred at all dose levels except the high dose group where decreased coagulation time was observed.
8. Clinical chemistry and urinalysis were not remarkable.

Toxicity Observed in Fischer Rats Treated Per Os for
28 Consecutive Days with Crude Marijuana Extract

Site: MRI, Worcester MA 01608
 Study # and Date: MRI-MH09-71-20, 12/30/70-2/3/71
 Contract No HSM-42-70-95
 Species and Strain: Fischer rats
 # of Rats/Level: 40/sex control, 20/sex for 150 and 750 mg/kg, and 30/sex for
 1200 and 1500 mg/kg
 Dose Levels: 0, 150, 750, 1200 and 1500 mg/kg
 Treatment Vol: 0.5 ml/100 gm B.W.
 Route: gavage (sesame oil)
 Duration: 28 days

Observation Parameters: Identical to Study #MRI-MH06-71-16 (12/16/70-1/20/71)
 i.e., 28 consecutive days with Delta-9-THC

Results:

1. Pharmacotoxic signs were essentially identical to those described for Delta-9- and Delta-8-THC, i.e., initial CNS depression followed by hyperactivity and fighting behavior as tolerance developed. A low

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incidence of tremors was also observed in rats treated with 750 or 1200 mg/kg day and one rat treated with 1500 mg/kg day exhibited clonic convulsions.

2. Mortality was dose related, i.e., 4/40 at 750 mg/kg, 18/60 at 1200 mg/kg and 44/60 at 1500 mg/kg.

Mortality of Fischer Rats Treated With CME
p.o. for 28 Days

Dose (mg/kg)	0	150	750	1200	1500
Mortality	0/80	0/40	4/40 [2 M + 2 F]	18/60 [8 M + 10 F]	44/60 [20 M + 24 F]

3. Treated animals showed weight loss initially; at termination body weight gain was depressed. The body weight changes did not appear to be related in severity to decreased food intake. Water consumption was slightly increased.
4. Histopathology revealed hypocellularity of bone marrow and spleen and vacuolization of the adrenal cortex in treated rats. Degeneration of seminiferous tubules was seen in 750 and 1200 mg/kg males. Treated rats also showed a dose related loss of abdominal fat and a decrease in exanguinable blood.

		<u>TNC*</u>			
		<u>0</u>	<u>150 mg/kg</u>	<u>750 mg/kg</u>	<u>1200 mg/kg</u>
M	18.32 ± 3.34	13.65 ± 0.71	25.92 ± 2.56 (N = 3)	18.94 ± 2.63 (N = 4)	
F	17.70 ± 1.72	17.58 ± 1.46	20.73 ± 1.37 (N = 4)	30.77 ± 11.46 (N = 2)	

*TNC in 10^6 cells/mg bone marrow, N - 5/sex/group except where specified.

5. Absolute and relative weights of testes, prostate, ovary, and uterus were decreased but adrenal glands were consistently increased in size.
6. BUN and coagulation time were slightly to moderately elevated in treated rats.

Chronic Toxicity

Toxicity Observed in Fischer Rats Treated Per Os for 119 Consecutive Days with Delta-9-THC

Site: MRI, Worcester, MA 01608
 Study # and Date: MRI-MH15-71-36, 12/23/70-6/10/71
 Contract No. HSM-42-70-95 and HSM-42-71-79.
 Species/Strain: Fischer rats
 # of Rats/Level: 40/sex for control, 20/sex for 50 and 250 mg/kg, 30/sex for 400 and 500 mg/kg
 Dose Levels: 0, 50, 250, 400 and 500 mg/kg
 Treatment Vol.: 0.5 ml/100 gm B.W.
 Route: gavage (sesame oil)
 Duration: 119 days
 Sacrifice Schedule: 5/sex/dose were sacrificed on Day 91, 105 and 119.

Observation Parameters:

Body weights were recorded on day 1 and weekly thereafter while rectal temperatures and respiration rates were measured five hours post treatment on days 1, 7, 56 and 91. Behavioral and clinical observations were made 5 hours post-treatment on days 1, 7, and weekly thereafter for the duration of treatment. Urinalysis, hematology and blood chemistry were done on days 28, 91, 105 and/or 119. Histopathological evaluations were performed by the end of the study.

Results:

1. The usual Delta-9-THC pharmacotoxic signs for this species were observed. Tolerance to depressant effects were observed beginning on the third day of treatment. Tolerant animals then began to show signs of hyperactivity and fighting behavior as described in the 28 day study. Tolerance to the stimulant effects was never seen. In fact, tremors occurred low incidence between days 20 and 30. These were manifested as coordinated spasms of the neck, eyes, mouth and forepaws. The severity of tremors gradually progressed to clonic convulsions which were dose related in frequency and onset first seen around Day 50. Continued treatment exacerbated these seizures. About 5-10% of the rats eventually showed tonic seizures. The convulsive activity was not reversible; tolerance to convulsive activity was not observed.
2. Mortality was dose related among the two highest dosage groups, i.e. 15/60 at 400 mg/kg and 50/60 at 500 mg/kg.

Mortality of Fischer Rats Treated With Delta-9-THC
p.o. for 119 Days

Dose (mg/kg)	0	50	250	400	500
Mortality	0/80	0/40	0/40	15/60	50/60
				[7 M + 8 F]	[21 M + 29 F]

3. All treated rats showed weight gain depression after 77 days as seen in the 28 day study. This was also seen at Day 105 in all but the highest dose group (no data available due to high mortality). Weight gain depression was also reported in the 50 and 250 mg/kg groups on Day 119.
4. Food and water consumptions were increased by 8-25% in treated groups on Day 90 and 105 with the females more severely affected on Day 105 (15-45% increases).
5. On Day 91, respiration rate was still depressed (10-20%) while rectal temperatures were either within normal limits or slightly depressed. No measurements on these parameters were done at the end of the study. (No summaries on food and water consumption, temperature and respiration were given).
6. Histopathology after necropsy on Day 91, 105, and 119 revealed hypocellularity and fat infiltration of the bone marrow and hypocellularity of the spleen among the 250, 400 and 500 mg/kg groups. Vacuolization in the adrenal cortex and testicular degeneration were also observed, but they were either not seen at each necropsy period or of low incidence.

Histopathology

Necropsied Day 91

	<u>0</u>		<u>50 mg/kg</u>		<u>250 mg/kg</u>		<u>400 mg/kg</u>		<u>500 mg/kg</u>	
	Severity* M	% F	Severity* M	% F	Severity* M	% F	Severity* M	% F	Severity* M	% F
Spleen, lymphocyte decrease							+	60 20	+	100
Adrenal, cortex vacuolization	(+)	20 10					+	20	++	20
Bone marrow, hypocellularity fatty infiltration	(+)	50 50	+	40 40	+	40 80	+	20 60 60 80	++	80 80
Testicular degeneration	+	10	+	20					++	20

Necropsied Day 105 or 119

	Day 105		Day 119		Day 119 50 mg/kg		Day 119 250 mg/kg		Day 105 400 mg/kg		
	Severity*	%	Severity*	%	Severity*	%	Severity*	%	Severity*	%	
Spleen, lymphopenia	0	0	0	0	+	20	+	60	+	40	60
Adrenal, cortical vacuolization					+	20	+	80			
Bone marrow, hypocellularity							+	60	++	60	80
fatty infiltration							+	100	++	80	60
lymphoid infiltrate									+		10
Testicular degeneration	+	20									

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe,
 No entry = no visible lesion

		<u>TMC*</u>				
		<u>0</u>	<u>50 mg/kg</u>	<u>250 mg/kg</u>	<u>400 mg/kg</u>	<u>500 mg/kg</u>
Day 91	M	23.3 + 3.1 (N = 20)	28.0 + 5.2 (N = 10)	37.7 + 14.4 (N = 9)	21.5 + 2.7 (N = 9)	17.4 + 3.5 (N = 8)
	F	34.8 + 4.5 (N = 20)	33.4 + 6.0 (N = 9)	24.0 + 4.87 (N = 10)	22.6 + 10.1 (N = 10)	
Day 105	M	28.1 + 7.7 (N = 5)			15.7 + 2.2 (N = 6)	
	F	14.6 + 1.3 (N = 4)			11.7 + 2.0 (N = 4)	
Day 119	M	37.4 + 7.7 (N = 5)	31.1 + 3.0 (N = 5)	28.3 + 2.4 (N = 5)		
	F	22.6 + 3.1 (N = 5)	42.7 + 2.2 (N = 4)	24.4 + 2.7 (N = 3)		

*TMC in 10⁶ cells/mg of bone marrow.

7. Organ weight changes included increases in absolute and relative adrenal weights at all dose levels and decreases in spleen and uterus weights in all treated groups.
8. Hematology and clinical chemistry revealed no apparent adverse drug related changes.

Toxicity Observed in Fischer Rats Treated Per Os for
119 Consecutive Days with Delta-8-THC

Site: MRI, Worcester, MA 01608
 Study # and Date: MRI-MH16-71-41, 12/30/70-6/10/71
 Contract No. HSM-42-70-95 and HSM-42-71-79
 Species/Strain: Fischer rats
 # of Rats/Level: 40/sex for control, 20/sex for 50 and 250 mg/kg, 30/sex for 400 and 500 mg/kg.
 Dose Levels: 0, 50, 250, 400 and 500 mg/kg
 Treatment Vol. 0.5 ml/100 gm B.W.
 Route: gavage (sesame oil)
 Duration: 119 days
 Sacrifice Schedule: 5/sex/dose were sacrificed on Day 91, 105 and 119.

Observation Parameters:

Identical to Study # MRI-MH15-71-36 (12/23/70-6/10/71), i.e., 119 day study of Delta-9-THC in Fischer rats.

Results:

1. Pharmacotoxic signs observed were essentially identical to those observed after administration of Delta-9-THC, i.e., initial CNS depression followed by hyperactivity and fighting behavior as tolerance developed. Tremors occurred in all groups and progressed gradually to clonic convulsions and eventually tonic convulsions. Tolerance to convulsive activity was not observed. The severity of convulsions increased as the duration of treatment was extended.
2. Doses of 400 mg/kg and up produced dose related mortality, i.e., 11/60 at 400 mg/kg and 23/60 at 500 mg/kg.

Mortality of Fischer Rats Treated With Delta-8-THC
p.o. for 119 Days

Dose (mg/kg)	0	50	250	400	500
Mortality	0/80	0/40	0/40	11/60	23/60
				[7 M + 4 F]	[3 M + 20 F]

3. Absolute and relative organ weights were both increased for adrenal, prostate, and liver and both decreased for uterus, spleen and pituitary.

4. Otherwise the usual toxicologic parameters were essentially similar to those observed after 119 days of treatment with Delta-9-THC, e.g., decreased weight gain, increased food and water consumptions late in the treatment, hypocellularity and fatty infiltration of the bone marrow and spleen, vacuolization in the adrenal cortex, stromal degeneration in ovaries and a dose related loss of abdominal fat.

Histopathology

	<u>0</u>		<u>50 mg/kg</u>		<u>250 mg/kg</u>		<u>400 mg/kg</u>		<u>500 mg/kg</u>			
	Severity*	%	Severity*	%	Severity*	%	Severity*	%	Severity*	%		
Spleen, lymphopenia												
Bone marrow, hypocellularity			+	20			+	20	20			
fatty infiltration	(+)	50	50	+	20	60	+	20	40	+	20	60
Ovary, stromal degeneration							(+)	20				
Adrenal, cortical vacuolization	(+)	20	10				+	20	20			
Sinusoids enlarged										+	20	20
Cortical fat deposit										+	20	

Hecropsted Day 91

N-18651-2

Necropsied Day 105 or 119

	Day 105		Day 119 50 mg/kg		Day 119 250 mg/kg		Day 105 400 mg/kg		Day 119 500 mg/kg	
	Severity*	%	Severity*	%	Severity*	%	Severity*	%	Severity*	%
Spleen, lymphopenia hematopoiesis	0		+	25			+	20	(+)	25
	M 5	F 4	M 4	F 3	M 5	F 5	M 5	F 4	M 4	F 4
Bone marrow, hypocellularity fatty infiltration (+)		25	+	50			(+)	20	+	25
Ovary, stromal degeneration			+	100	+	60			+	75
Adrenal, cortical vacuolization			+	25	33	+	40	40	+	25
Sinusoids enlarged							+	80	+	25
Cortical degeneration									+	25
Congestion									+	75
Cortical fat deposition									+	50

*Rating of changes, (+) slight; + moderate; ++ marked; +++ severe; ++++ very severe,
No entry = no visible lesion

		<u>TNC*</u>				
		<u>0</u>	<u>50 mg/kg</u>	<u>250 mg/kg</u>	<u>400 mg/kg</u>	<u>500 mg/kg</u>
Day 91	M	23.3 + 3.1 (N = 20)	45.1 + 9.2 (N = 10)	37.9 + 7.5 (N = 10)	19.7 + 2.3 (N = 10)	27.7 + 1.7 (N = 10)
	F	34.8 + 4.5 (N = 20)	25.3 + 3.2 (N = 10)	26.0 + 3.6 (N = 10)	20.2 + 3.1 (N = 12)	30.8 + 6.6 (N = 5)
Day 105	M	28.1 + 7.7 (N = 5)			23.0 + 3.6 (N = 5)	
	F	14.6 + 1.3 (N = 4)			13.9 + 0.6 (N = 4)	
Day 119	M	37.4 + 7.7 (N = 5)	43.6 + 12.8 (N = 5)	26.6 + 4.7 (N = 5)		16.8 + 3.2 (N = 4)
	F	22.6 + 3.1 (N = 5)	25.1 + 7.8 (N = 3)	24.9 + 8.1 (N = 5)		25.2 + 5.3 (N = 4)

*TNC in 106 cells/mg of bone marrow.

Toxicological Manifestations in Fischer Rats Treated Orally with
Delta-9-THC at Doses Equivalent to American Marijuana
and Hashish for 28 Consecutive Days (Interim Report)

Site: MRI, Worcester, MA 01608
Study # and Date: MRI-MH03-71-41, 6/21/72-9/29/72
Contract No. HSI-42-71-79
Species/Strain: Fischer rats
of Rats/Level: 48 rats/sex/level
Dose Levels: 0, 2, 10, and 50 mg/kg

Dose Selection Rationale:

[REDACTED]

Treatment volume: 1.0 ml/100 gm B.W.
Route: gavage (sesame oil)
Duration: 28 days
Sacrifice Schedule: 6/sex, control and high dose sacrificed on Day 15,
6 sex, control and high dose sacrificed on Day 29 -
rest remaining on study to 90 and 180 days.

Observation Parameters:

Behavioral observations were performed daily in the morning and afternoon. Clinical measurements of respiration rate, rectal temperature, activity, body weight and food and water consumption were carried out once a week. Urinalysis, hematology, blood chemistry and neurochemistry were done on day 28. Hormonal measurements and histopathology evaluation were carried out on days 14 and 28.

Results:

1. Treated rats showed the usual CNS depression in the first week of treatment. A dose-related decrease in respiration rate occurred. With the onset of tolerance in the second week, hypersensitivity and passivity became apparent and depressant effects were reduced. Irritability and fighting occurred at higher doses in the third week. Aggression was found to be associated with territorial establishment and was more apparent at 10 mg/kg than 50 mg/kg.

2. A poikilothermic effect was observed in response to higher ambient room temperatures.
3. Diminished food and water consumption in conjunction with body weight gain depression occurred in the second and third weeks but these were not evident after 4 weeks of treatment.
4. At high doses adrenal weights were elevated in both sexes and pancreas in males. Decreases in prostate and uterus weights were also discerned with a possible fall in female pituitary weight.
5. Gross and histopathology, hemochemistry and urinalysis revealed no apparent drug related changes.
6. Neurochemistry of the brains of treated rats revealed no definite trends.

Toxicological Manifestations in Fischer Rats Treated Orally with
Delta-9-THC at Doses Equivalent to American Marijuana and
Hashish for 90 Consecutive Days (Interim Report)

Site: MRI, Worcester, MA 01608
Study # and Date: MRI-MH04-72-51, 9/30-11/30/72
Contract No. HSM-42-71-79
Species/strain: Fischer rats
of Rats/Level: 48 rats/sex/level
Dose Levels: 0, 2, 10, and 50 mg/kg
Treatment Vol: 1.0 ml/100 gm B.W.
Route: gavage (sesame oil)

Duration: 90 days

Observation parameters: identical to study #MRI-MH03-71-41 (6/21-9/29/72) except that the treatment duration was 90 days. In addition a Tolerance Study was carried out under this study #.

Tolerance Study:

Species/Strain: Fischer rats
of rats/level: 6 rats/sex for control and 18 rats/sex/level for the treated groups.
Dose Levels: 0, 10, 20, 40 and 80 mg/kg.
Route: gavage (sesame oil)

Duration: The following treatment durations for each level were established according to tolerance developments during the study:

10 mg/kg	--	Days 1-10
20 mg/kg	--	Days 11-15
40 mg/kg	--	Days 16-23
80 mg/kg	--	Days 24-30

Behavioral Observations:

1. Undisturbed behavior -- locomotor activity, body position, ptosis, lacrimation, tremors, convulsions and bizarre behavior.
2. Manipulative observations -- transfer arousal, ataxia, ptosis, relaxation, hypersensitivity, pinna reflex, corneal reflex, visual placing, wire maneuver, righting reflex, passivity, irritability and tremors.

In addition to behavioral assessments, exploratory activity, body weight, rectal temperature and respiration were also monitored.

Results:

1. Behavioral changes observed were similar to that observed for the 28 day study of Delta-9-THC (p.o.) at doses equivalent to American marijuana and hashish, i.e., initial CNS depression followed by hypersensitivity, hyperactivity, irritability and aggression, as tolerance developed. Additional toxic signs seen in this study included hypnotic trances, tremors and convulsions. Fighting was more prevalent in males (75%) than in females (51%) and peaks of fighting occurred near days 22 and 34 at 10 mg/kg and at day 60 at 50 mg/kg. The incidence of fighting was inversely dose related. Fighting fell considerably by the end of the study (day 90). Hypnotic trance, and tremors and convulsions appeared approximately by day 70. The incidence of tremors and convulsions was dose-related and increased progressively with time.
2. Mortality occurred in 2/66 of the 2 and 10 mg/kg groups and deaths were due to aspiration of drug into lungs. Two other rats were sacrificed on day 15 and 18 due to gaseous block in the duodenum causing back pressure on the lung and difficulty in breathing.
3. Treated rats showed a dose-related decrease in rate of growth at the higher doses. Food consumption was increased in the 50 mg/kg group throughout the 90 days of treatment. The initial reduction in water consumption during the first month of treatment, however, was reversed with continued treatment.

4. Respiration rate was still depressed during the current interval of treatment. The incidence of respiration rate depression was higher for the females than the males. Mean rectal temperature appeared normal.
5. Organ weights of brain, kidney, adrenal, testes and male pancreas appeared increased and female pituitary and male prostate decreased at higher dose levels.
6. Serum growth hormone levels increased 22-139% in both sexes after 14 days of treatment but decreased 11-38% after 28 days of Delta-9-THC administration. Serum FSH levels increased 84-100% in females by day 14 and remained elevated 16-52% on day 28.
7. Brain neurochemistry revealed small (6-8%) but significant decreases in RNA and AChE in the frontal cortex and cerebellum from rats given 2 mg/kg and in most portions of brain (3-12%) after the administration of the higher doses. At 50 mg/kg, protein also declined.
8. Hemochemistry, urinalysis and histopathology were essentially normal.
9. Thirty-day Tolerance Study revealed that the onset and duration of behavioral changes decreased as the dosages of Delta-9-THC increased. In undisturbed rats, the # of animals involved in aberrant behavior increased progressively as dosage of Delta-9-THC doubled. Among the manipulative observations, maximal passivity occurred at 10 mg/kg, irritability at 20 mg/kg, abnormal transfer arousal, hypersensitivity, corneal reflex and wire maneuver at 40 mg/kg, and ptosis, relaxation, pinna reflex, visual placing and bizzare behavior at 80 mg/kg. Sex differences were minimal.

Toxicological Manifestations in Fischer Rats Treated Orally With
Delta-9-THC at Doses Equivalent to American Marijuana and
Hashish for 180 Consecutive Days (Final Report)

Site: MRI, Worcester, MA 01608
 Study # and Date: MRI-MH01-73-3, 6/21/72-3/9/73
 Contract No. HSM-42-71-79
 Species/Strain: Fischer Rats
 # of Rats/Level: 48 rats/sex/level
 Dose Levels: 0, 2, 10 and 50 mg/kg
 Route: gavage (sesame oil)
 Duration: 180 days with interim sacrifices done on Day 14, 28, 90 and 180

Observation Parameters: identical to Study #MRI-MH04-72-51
 (9/30-11/30/72), i.e., 90 days interim report.

Results:

1. Pharmacotoxic signs observed up to 90 days of treatment were described in the previous interim reports (28 days and 90 days). Extension of treatment to 180 days was found to be associated with a decrease in fighting incidence to 20% from days 100-180 and involved primarily animals which had not fought previously. Furthermore, a delayed response of brief and sporadic fighting and hyperactivity was found to occur in rats treated with 2 mg/kg Delta-9-THC between days 128-142. Hypersensitivity, excess grooming, hyperactivity and hypnotic trance which were observed after the initial CNS depression disappeared essentially upon prolonged treatments. Exploratory activity increased 100% at 50 mg/kg from days 93-120. Tremors and convulsions appeared in a cyclic fashion peaking in weeks 12, 18 and 21 with the highest peak occurring at week 18. The incidence of convulsions was 50% at 50 mg/kg and 6% at 10 mg/kg.
2. Three high dose rats per sex died following convulsions; three additional high dose rats succumbed following dosing accidents. One low dose male died after 175 days of treatment from a pulmonary hemorrhage. Histopathology examination did not provide cause of death for those rats which died from convulsions.

Mortality of Fischer Rats Treated with Delta-9-THC
p.o. for 180 Days

<u>Dose (mg/kg)</u>	0	2	10	50
	0/96	1/96 [IM]	0/96	9*/96 [3 M + 3 F]

*3 rats died following dosing accident.

3. Treated rats showed reduced weight gains and increased food consumption. Water consumption was also increased in females. Body temperature was not affected by drug treatment.
4. Respiration rate was decreased 15-30% at 50 mg/kg for both sexes from days 100-119. Thereafter respiration rate was either normal or slightly depressed.
5. The greatest organ weight changes occurred at 50 mg/kg; among the increases were adrenals (45%), male pancreas (96%), testes and prostate (13-25%), and brain, lungs, kidneys, heart and liver (10-20%); female pituitary decreased by 50%.
6. Mid and high dose females showed elevated serum LH and FSH (60-180%) at the 14 day assay interval. At 28 days LH and FSH were still increased but was of lesser magnitude. By day 90 both hormones returned to control values.

7. Neurochemical changes obtained at 180 days were more evident than those at 90 days. Decreases of 10-40% occurred in protein and RNA in various portions of the brain in both sexes at all dose levels. AChE activity was predominantly depressed in the female.
8. SGOT and SGPT were increased 28-45% and 46-69% respectively in males at higher doses.
9. Clinical chemistry, hematology, urinalysis, gross and histopathology were unremarkable.

Reproduction Studies

I. Rat

Reproduction Study with Delta-9-THC in Albino Rats

Site: Industrial Bio-Test Laboratories, Inc.
1810 Frontage Road, Northbrook, Ill 60062

Study Number and Date: IBT No. B287B, September 21, 1972
Contract No. HSM-42-71-106

Species/Strain: Charles River Strain Albino Rats.
No. of Animals/Level: 10 males and 20 females/level

Dose levels: 0, 0.5, 1.5, and 5.0 mg/kg.

Route: gavage (sesame oil)

Treatment Duration:

Males- at 40 days of age and continued daily until the completion of mating period (a total of 105 days)

Females Two weeks prior to mating (100 days of age) through gestation and lactation.

Results:

1. Pharmacotoxic signs observed among animals from all treatment groups included inactivity, characterized by slow movements and wide stance, a tendency to crouch and grasp the cage floor, irritability, pallor and pupillary constriction. The severity and duration of these reactions were dose related. An apparent tolerance was manifested by a decrease in the severity and duration of these reactions.
2. One control male and one low dose female died after weaning. Death was attributed to severe respiratory infection.
3. Mid and high dose males showed dose related weight gain depression throughout the 105 days pre-mating and mating period. Weight gain depression in females was seen only in the HD group and only during the 14 day pre-mating period.

4. Food consumption was not adversely affected by drug treatment.
5. Mating and fertility indices, and reproductive indices (gestation time and incidences of pregnancy and parturition) were similar for the control and all treatment groups.
6. The no. of corpora lutea, implantation sites, resorption sites and viable fetuses were similar for all groups at the interim sacrifice (the 14th day of pregnancy).
7. At lactation day 12 and a weaning a significant decrease in the no. of viable pups was seen in the high dose group. This was also seen, to a lesser degree, in the MD group.

Progeny Population Data
(Mean Values)

<u>Group and Dose level</u>	<u>#of pups Born Viable</u>	<u>#of pups Viable at Lact day 1</u>	<u>#of pups at Lact Day 4 Viable Retained</u>	<u>#of pups Viable at Lact day 12</u>	<u># of weanlings Mean/Litter</u>
Control	12.7	12.7	10.2	8.8	5.9
0.5 mg/kg	11.5	11.1	10.4	9.1	7.8
1.5 mg/kg	11.9	11.5	7.5	7.4	4.2
5.0 mg/kg	10.9	10.9	7.0	6.5	3.6

8. The 4-day survival, 12 day survival and lactation indices of mid- and high-dose pups were reduced. Pup weights were not adversely affected by drug treatment.

Survival Indices

<u>Group and Dose Level</u>	<u>Live Birth</u>	<u>24 Hour Survival</u>	<u>4 Day Survival</u>	<u>12 Day Survival</u>	<u>Lactation</u>
Control	100.0	100.0	80.7	74.7	67.1
0.5 mg/kg	100.0	96.5	90.4	90.1	85.7
1.5 mg/kg	96.6	96.6	63.0	68.9	56.8
5.0 mg/kg	97.3	99.1	64.2	55.4	55.4

Teratogenic Study with Delta-9-THC in Albino Rats

Site: Industrial Bio-Test Laboratories, Inc.

Study No. and Date: IBT No. B267D September 21, 1972

Contract No. HSM-42-71-106

Species/Strain: Charles Rivers Rats

No. of Pregnant rats/level: 20 control, 19 mid and high dose, 18 low dose.

Dose Levels: 1, 5, 15, 50 mg/kg

Route: gavage (sesame oil)

Treatment Duration: Day 6-15 of gestation with sacrifice on Day 20.

Results:

1. Abnormal behavioral reactions observed among all Delta-9-THC treatment groups were identical to those previously described for the species in the reproduction study. Tolerance occurred after the first three to five doses. However, the pharmacotoxic signs never disappeared completely.
2. All control and treatment dams survived the study.
3. Treated dams showed dose related weight gain depression. The weight gain depression of low dose females was most apparent between days 9 and 12 while mid- and high-dose females showed most severe weight reductions during days 6-9.
4. The numbers of corpora lutea, implantation sites resorption sites and viable fetuses were not affected by drug treatment.
5. Except for an increase in incompletely ossified sternum sections in offspring of mid- and high-dose dams, no apparent drug related gross, skeletal or visceral anomalies were observed.

Perinatal and Lactation Performance Study with Delta-9-THC in Albino Rats

Site: Industrial Bio-Test Laboratories, Inc.

Study No. and Date: IBT No. B287F, September 21, 1972

Contract No. HSM-42-71-106

Species/Strain: Charles River Rats

No. of Dams/level: 19 control, 20 treated

Dose Levels: 0, 0.5, 1.5, and 5.0 mg/kg

Route: gavage (sesame oil)

Duration: Day 15 of gestation through lactation (total of 28 or 29 doses).

Results:

1. Pharmacotoxic signs and patterns of tolerance were identical to those previously described for this species.
2. One low dose female died of an acute respiratory infection prior to delivery.
3. High dose dams exhibited a slight depression in body weight between the initiation of dosing and day 12 of lactation.

7. The number of pups delivered and viable at birth was not affected by drug treatment. However, the numbers of pups alive on days 4, 12 and 21 were significantly lower in the high dose group. The corresponding survivals for mid-dose pups were slightly lower than those for controls.
5. A reduction in the number of pups weaned was observed in high dose dams. A slight decrease in this parameter was also seen in the mid-dose group.
6. Pup weights were not affected by drug treatment.
7. The pups showed neither abnormal behavior nor signs. No gross anomalies were observed.

Serum Hormone Levels and 30 Day Recovery of Fischer Rats Treated Orally
with Delta-9-THC for 180 Consecutive Days

Site: Mason Research Institute
23 Harvard Street
Worcester, Massachusetts 01608

Study No. and Date: MRI-MH02-73-14, 12/19/72 - 4/20/73
contract No. HSM-42-71-79

Species/Strain: Charles River Fischer Rats

No. of Animals/level: 48 rats/sex/dose

Route: Gavage (sesame oil)

Dose Levels; 0, 2, 10, and 50 mg/kg

Treatment Vol: 1 ml/100 gm B.W.

Duration: 180 days

Recovery period: 30 days (drug free)

Sacrifice Schedule: 6 rats/sex/treatment at 14, 28, 90 and 180 days of
treatment

Observations: behavioral and physiological parameters, brain RNA, protein and
AChE activity, Serum GH, FSH and LH levels and histopathological
evaluation (vehicle control and HD group).

Results:

1. No behavioral or clinical abnormalities were observed during recovery period.
2. Despite a normal growth rate for all groups food consumption was increased 10-15% for both sexes and water intake 3-20% for females.
3. Hemochemical changes were minor but blood sugar was elevated 15-69% for both sexes. This hyperglycemia effect might be related to the restoration of depleted liver glycogen stores.

4. Urinalysis and histopathological findings were within normal limits.
5. Organ weight changes included a 30% increase in male pancreas and pituitary and a 20% rise in adrenals of both sexes.
6. Serum hormones FSH, LH and GH had returned to normal before treatment was terminated except for an elevated male FSH level.
7. Neurochemical changes involved a 10% decrease in cerebral protein, a 14-21% decline in male cerebellar RNA and a 22-67% increase in female cerebellar AChE.

Serum Hormone Levels in Pregnant Fischer Rats Treated Orally With Delta-9-THC
- Status Report, MRI-MH02-74-6, 11/1/73-2/8/74, Contract HSM 42-71-79
 and

Serum Hormone Levels in Non-Pregnant and Pregnant Fischer Rats Treated Orally
with Delta-9-THC - Final Report MRI-DA05-74-17, 2/8-6/7/74, Contract
HSM-42-71-79

Site: MRI, Worcester, Mass.

Species/Strain: Charles River Fischer Rats

No. of Non-pregnant females/phase of estrous cycle: 10-12

No. of Pregnant females/level: 40

Route: Gavage (sesame oil)

Dose Levels: 0, 1, 5, and 10 mg/kg; non pregnant controls

Treatment and Sacrifice Schedule:

10 pregnant rats/level were sacrificed after 6 or 12 days of treatment during gestation, or after 21-22 days through parturition or after 28 days of dosing to include the lactation period.

Observations:

Final body weights of dams, organ weight changes (pituitary, adrenals, and gonads and uterus), litter parameters at necropsy (no. of implants and pups, resorption, viability, and gross malformation) LH, FSH, estrogen and progesterone determinations.

Results:

1. Untreated, non-pregnant rats.

1. Final body weights and endocrine organ weights of various estrus phases did not differ from those of the estrus phase in the groups of rats used for estimation of LH and estrogen (status report). However, organ weight changes were observed in the groups used for the determination of FSH and progesterone (final report).

Organ Weight Changes in Non-Pregnant Rats

	Pituitary	Adrenals	Uterine
Estrus	-	-	-
Metestrus	40%	-	-
Diestrus I	40%	11%	20%
Diestrus II	30%	11%	12%
Proestrus	30%	-	12%

Final body weights and ovarian weights remained unchanged for these latter groups.

2. Hormone changes were as follows:

	LH	FSH	Estrogen	Progesterone
Estrus	--	--	--	--
Metestrus	62%	42%	--	--
Diestrus I	98%	65%	64%	95%
Diestrus II	23%	73%	--	26%
Proestrus	--	56%	75%	65%
				42%

II. Pregnant Rats

1. Maternal weight gains and litter parameters (no. of implants and pups, resorption, viability and gross malformation) were not adversely affected by drug or duration of treatment. In the 5 mg/kg and 10 mg/kg groups, 1/100 pups was a runt.
2. Pituitary, adrenal and ovarian weights were not adversely affected by drug treatment.
3. Serum FSH, LH, estrogen and progesterone were not affected to a consistent degree by drug treatments either in terms of dose or duration. Individual variation, diurnal surges and placental contribution effectively masked the effects of Delta-9-THC if such exists.

The Effects of Delta-9-THC on Pregnancy and Fetal Mortality in Mice and Rats*

Site: MRI, Worcester, Mass 01608

Study No. and Date: MRI-DA01-75-3, 10/15/74-1/31/75

Contract No. HSM-42-71-79

Species/Strain: Charles River Fischer Rats.

No. of Pregnant rats/level: 50

Route: gavage

Dose Levels: 0 (sham-treated controls, sesame oil controls) 12.5, 25, and 50 mg/kg

Treatment and Sacrifice Schedule: 10/treatment were sacrificed

<u>No. of treated days**</u>	<u>No. of drugless days</u>	<u>Sacrifice Gestation Day</u>
2	---	8
5	---	11
8	---	14
10	1	17
10	3	19

**First day of treatment was Day 6 of gestation.

Results:

A. Overall findings

1. High dose animals were sedated and vocalized after the first dose. Depression was seen after the second and third doses. About one-half of the low- and mid-dose dams showed depression after the first and second doses. Some mid-dose animals vocalized also. After five days of treatment about one-half of the low- and mid-dose dams became aggressive and had to be separated.
2. 1/54 sham treated and 2/50 high-dose rats died. These deaths were not attributed to THC. No information was presented regarding cause of death.
3. The pregnancy rates in Delta-9-THC groups (79%) were significantly different from controls (91%) but no differences among Delta-9-THC groups were observed.
4. Body weights and uterine weights of dams fell in the treated groups. More dams exhibited early resorptions in treated groups.
5. Four percent of the Delta-9-THC treated dams showed a blood stained perineum (none in the controls).
6. The number of viable fetuses among all treated groups was decreased, all fetal deaths were early resorptions. Fetal mortality was 22% (12.5 mg/kg); 20% (25 mg/kg); 35% (50 mg/kg) and 4% in controls.

B. Temporal pattern.

Treatment

Gestation Day	Maternal and Litter Effects
6-8	No adverse effects
6-10	Uterine weight losses, non-dose related early resorption, reduction in number of viable pups per litter and increased fetal mortality
6-13	Same as above. Fetal mortality among high-dose rats were significantly greater than that of controls and other treatment groups.
6-15 plus 1 or 3 drugless days	Same as above, in addition, conception rate was decreased.

An attempt was made to administer higher doses (75, 150, and 300 mg/kg Delta-9-THC, gavage) to three groups of pregnant rats. Deaths were seen among all groups necessitating a reduction in dosage.

*Results on mice are presented under the species heading of mice.

The Effects of Delta-9-THC on Pregnancy and Fetal Mortality in Rats Established Pregnant by Laparotomy

Site: MRI, Worcester, Mass 01608

Study No. and Date: MRI-DA03-76-12, 1/19-3/31/76

Contract No. HSM42-7179

Species/strain: Charles River Fischer 344 rat.

No. of pregnant rats/group: 27

Route: gavage (sesame oil)

Dose Level: 0 (sham-treated controls, sesame oil controls) and 50 mg/kg

Treatment Vol: 0.5 ml/150 gm B.W.

Duration: Days 6-9 of gestation.

Sacrifice Schedule: Fifteen and 12 rats, respectively, were sacrificed from each group on days 12 and 16 of gestation.

Results:

In the Delta-9-THC treated groups, a significant increase in fetal mortality and whole litter resorption occurred.

1. In controls, fetal mortality averaged 7.7%, while in treated rats it was increased to 27.1% and 46.9% at 12 and 16 days of gestation, respectively.

2. Whole litter resorption occurred in 9/27 Delta-9-THC treated dams in sharp contrast with 0/54 control dams. Among these 9 dams, four showed remnants of prior implantation and five showed no vestige of prior implantation.
3. Among fetal resorptions, 54.3% remnants of implantation could be seen whereas 45.7% no visible vestige of prior implantation could be detected (complete resorption).

Effects of Long Term Oral Treatment of Delta-9-THC on the Male Rat Reproductive Endocrine System

Authors and Site: G.I. Fujimoto, G.A. Morrill, A.B. Kostellow,
R.M. Rosenbaum and D. Ziegler
Depts. of Biochem., Physiology and Pathology
Albert Einstein College of Medicine
Bronx, N.Y. 10461

Study No: Contract No. 271 76 3318, National Institute on Drug Abuse

Species/Strain: Fischer rats.

No. of rats/level: 10-12 male rats/level.

Route: oral intubation

Dose Levels: Group I: 1 mg/kg

Group II: 5 mg/kg

Group III: 25 mg/kg

Group IV: [REDACTED]

Group V: Untreated Control

Treat Volume: 0.5 ml/100 gm B.W.

Duration: 77 days (10-11 weeks).

Results:

1. At the mid and highest dosages, ventral prostate weight decreased 19% (II) and 51% (III) respectively (p value is less than 0.01). At the highest dosage epididymal weight was 34% less and seminal vesicle 47% less than intubated control (p value is less than 0.01). Seminal fluid volume was depressed 10% (II) and 42% (III) while fructose content was 23% (II) and 52% (III) less than vehicle control values (p value is less than 0.01).
2. Delta-9-THC treatment did not affect serum testosterone levels in the low (I) and high (III) dose groups. However, there was a two-fold increase in the mid dose (II).
3. No effects on sperm count in the cauda epididymis, mating success and offspring in weight and gross appearance were observed.

4. In the testis, at 25 mg/kg, there were areas with sparsity of Leydig cells in the interstitium and a decrease in spermatogenesis and number of developing germ cells in a less organized spermatogonia layer in the seminiferous tubules. However, sufficient areas of normal Leydig cells population remained to allow for production of normal to high levels of serum testosterone.

Acute Cytogenetic Effects of Single Oral Doses of Delta-9-THC on Female Sprague-Dawley Rats at Intervals of 6, 12, 18, 24, 48, and 96 Hours

Site: Case Western Reserve University Medical School
Cleveland, Ohio

Study No. and Date: "First Quarterly Report to NIMH on Contract HSM-42-72-166"
12/19/72

I. Bone Marrow Studies

Species/Strain: Sprague-Dawley rats
No. of Rats/Interval: 5 female rats/time interval
Time Intervals: 6, 12, 18, 24, 48, 96 hours post-treatment
Route: gavage (sesame oil)
Dose: Delta-9-THC, 50 mg/kg

Treatment Volume: 1 ml/200 gm B.W.

Colchicine was injected intraperitoneally at dose of 4 mg/kg 3 hrs. prior to sacrifice.

Observations: Chromosome aberration, mitotic index.

II. In vitro Microbial Assay

Tester Strains: his G46, his C 207, his C 3075, TA 1530, TA 1531, and TA 1532
(all are *S. typhimurium* LT-2 mutant strains).

Route: Direct application of the various treatments to the tissue culture plates.

- Dose:
1. Negative control (spontaneous reversion)
 2. Negative control
 3. Positive control
 4. Positive control
 5. Delta-9-THC, 0.2 and 1.0 mg/plate

Results:

1. Animals sacrificed at 18 hours post-treatment showed an aberration frequency of 3% for the Delta-9-THC treated group as compared to 1.0% for saline control; the aberrations seen in the THC group were mainly multiple breakages. No differences in aberration frequency were obtained at other intervals. In cytoxan-treated positive controls, the aberration frequency

increased progressively from 10% to 70% over a period of 24 hours then decreased sharply to 25% at 48 hours and returned to negative controls by 96 hours.

2. The mitotic index of Delta-9-THC treated rats 6 to 18 hours post-treatment, was slightly lower than negative controls. The cytoxan-treated animals exhibited intense mitotic inhibition from 6 to 48 hours post-treatment.
3. The Delta-9-THC treated rats showed a frequency of 10 to 14% of "sticky" metaphase chromosomes as opposed to less than 3% in negative controls.
4. No significant increases in reversion rates of histidine auxotrophs of S. typhimurium were observed when bacterial plates were treated with Delta-9-THC at concentrations of 0.2 and 1 mg/plate, as compared to negative controls; N-methyl-N-Nitro-N-nitrosoguanidine and ICR 191 showed the expected positive results.

II Mouse

The Effects of Delta-9-THC on Pregnancy and Fetal Mortality in Mice and Rats

Site: MRI, Worcester, 1 Mass 01608

Study No. and Date: MRI-DA01-75-3, 10/15/74-1/31/75

Contract No. HSM-42-71-79

Species/Strain: Charles River (CD-1) mice.

No. of pregnant mice/level: 90-95

Route: gavage

Dose Levels*: 0 (sham-treated controls, sesame oil controls) 150, 300 and 600 mg/kg

*Originally Delta-9-THC doses of 75, 150, 300 mg/kg were intended. However, because of a technical mistake, the higher doses were given.

Treatment volume: 1 ml/100 gm B.W.

Treat. and Sacrifice Schedule: 20-22/control, 20/treated group on Gestation days 8, 11, 14, and 17 sacrifices, 10/control and 10/treated group on gestation day 19 sacrifice.

<u>No. of treated days+</u>	<u>No. of drugless days</u>	<u>Sacrifice Gestation Day</u>
2	-	8
5	-	11
8	-	14
10	1	17
10	3	19

+First day of treatment was Day 6 of gestation.

Results:

A. Overall findings

1. Treated dams showed depression after the first two doses. After the third dose depression was less severe indicating, perhaps, tolerance development. High dose dams showed hyperirritability after 4 or 5 doses. Treated mice showed rough coats after 2 or 3 doses.
2. Mortality rates of dams are as follows:
 Sham control: 0/95
 Sesame oil: 5/94
 150 mg/kg: 4/90
 300 mg/kg: 7/90
 600 mg/kg: 6/90
 Deaths were primarily due to dosing accidents.
3. Treated dams showed dose related weight gain depression as well as dose-related decreases in uterine weights.
4. About 15-19% of the treated dams showed vaginal bleeding.
5. The conception rate in control mice was 61% and in Delta-9-THC treated groups: 34% (150 mg/kg), 24% (300 mg/kg) and 8% (600 mg/kg).
6. A dose related reduction in the number of viable fetuses as well as a dose related increase in fetal mortality were observed.

	<u>Sham</u>	<u>Sesame Oil</u>	<u>150mg/kg</u>	<u>Delta-9-THC 300 mg/kg</u>	<u>600 mg/kg</u>
#Viable/ litter	9.26±4.23	10.23±3.88	4.86±5.70	2.50±4.60	0
%Fetal Mortality	17	14	44	75	100

B. Temporal patterns.

Treatment
Gestation Day

Maternal and Litter Effects

- 6-8 Dose related decrease in uterine weights, in # of viable fetuses per litter and increase in fetal mortality (100% at HD). Vaginal bleeding among all treated groups (non-dose related).
- 6-10 Complete interruption of pregnancy at 600 mg/kg. Fetal mortality was 100% at all three dose levels. Three or four treated dams per level showed vaginal bleeding.

- 6-13 Weight gain depression in mid and high dose dams. Complete interruption of pregnancy at 600 mg/kg. Fetal mortality was increased and number of viable fetuses/litter reduced at 300 mg/kg.
- 6-15 plus Same as above. 100% fetal mortality occurred at day 17 and 1 or 3 drugless 19 sacrifices for the low dose. 33% and 100% respectively days for the mid dose. Completed interruption of pregnancy at the high dose.

Mouse Teratology Study with Delta-9-THC Administered Orally During Days 6-15 of Gestation (Interim) MRI-MH03-74-8, 1/7/74-2/28/74. Contract No. HSM-42-71-79

Mouse Teratology Study with Delta-9-THC Administered Orally During Days 6-15 of Gestation (Final Report) MRI-MH04-75-15, 2/2/74-4/8/74. Contract No. HSM-42-71-79.

Site: MRI, Worcester, MA
 Species/Strain: Charles River Albino Mice (CD-1)
 No. of pregnant females/level: 63-93
 Route: gavage (sesame oil)
 Dose Levels: 0, 5, 15, 50 and 150 mg/kg
 Treatment Volume: 0.5 ml/100 gm B.W.
 Duration: Day 6-15 of gestation with sacrifice 24-36 hours before natural parturition.

Acute LD50 Study

Species/Strain: Charles River Albino Mice
 No. of mice/sex/level: 6/sex/dose level
 Route: gavage (sesame oil)
 Dose Range: 400-6400 mg/kg
 Treatment Volume: 0.5 ml/mouse

Results:

1. The following maternal mortality rates were observed:

Vehicle Control:	5/66
5 mg/kg:	4/64
15 mg/kg:	5/82
50 mg/kg:	7/93
150 mg/kg:	0/63

The vast majority of the deaths was due to faulty gavage technique. Inconclusive diagnosis on some deaths was due to cannibalism.

2. A dose related induction of resorption was observed:

Vehicle controls:	1%
5 mg/kg:	11%
15 mg/kg:	15%
50 mg/kg:	29%
150 mg/kg:	56%

Resorptions were complete since no clear signs of implantation sites or resorptions were evident at necropsy.

3. Approximately 15% of the animals in each group (vehicle controls and the treated) delivered 1 to 4 days prematurely. Premature delivery was not related to Delta-9-THC treatment but instead may have been influenced by vehicle and/or manipulation of the mice during treatment.
4. There was no effect of Delta-9-THC on dam growth, number of implants (12-13), number of live pups (11-12) total litter weight (12.7-13.7 gm), pup weight (1.12-1.22 gm), and sex distribution. Less than 2% of fetuses were non-viable.
5. Gross abnormalities occurred in 2.2% of the vehicle and Delta-9-THC treated groups; soft tissue abnormalities, 17% for Delta-9-THC and 13% for vehicle; skeletal variations, 16% for Delta-9-THC and 8% for vehicle. Predominant abnormalities included: gross skin hemorrhages, curved hindlegs, edema, periorbital swelling; soft tissue hemorrhages, hydronephrosis, hydrocephalus; rib and sternal variations. Delta-9-THC induced a greater incidence of abnormalities but they were similar to those in vehicle controls.
6. Acute oral LD50 was 2240 and 1410 mg/kg for male and female, respectively.

The Effect of Intra-gastric Administration of Delta-9-THC on the Growth and Development of Fetal Mice of the A/J Strain.

Authors and Site: Eric Block, Gene A. Morrill, George I. Fujimoto
Albert Einstein College of Medicine
Bronx, New York 10461

Study No. and Date: Contract No. 271 76 3318, National Institute on Drug Abuse.

Species/Strain: A/J mice

No. of pregnant mice/level: 13 untreated, 25 vehicle-treated, and 69 THC treated (no details on each dose level and each treatment period were given).

Dose Levels: Untreated control; untreated, reduced food intake (deprived of food for 24 hours on Day 11 of gestation); Vehicle control, 60, 120 and 240 mg/kg Delta-9-THC.

Positive Controls: cortisone-acetate, 60 mg/kg i.p.
corticosterone, 60 or 120 mg/kg, I.M., N=10/group.

Route: Intra-gastric administration, [REDACTED]

Treatment Volume: 1 ml/100 gm B.W.

Treatment Duration: Days 11 and 12, 12 and 13, or 13 and 14 (240 mg/kg only) of gestation.

Sacrifice Schedule: Animals were sacrificed on Day 20 of gestation; a few mice were killed on Days 18 or 19.

Results:

1. In the untreated group there existed a temporal bimodality in the frequency of resorption; a rate of $5.9 \pm 11.8\%$ ($\bar{X} \pm S.D.$) during Jan, 1977 and of $23.6 \pm 17.3\%$ during Sept-Nov. 1977. This temporal bimodality was seen only in this group of animals.
2. Intra-gastric intubation of Delta-9-THC on Days 11 and 12 of gestation produced no effects on number of live births, incidence of resorption, and spontaneous cleft palate formation ($7.1 \pm 12.6\%$ fetuses/litter for A/J mice). However, an incidence of 2.5-5.7% of open eyelids was observed.
3. Treatment on days 12 and 13 resulted in a decreased rate of live births, an increased frequency of resorptions (THC greater than vehicle intubation which in turn greater than untreated) and a dose related increase in mean frequency of cleft palate formation (statistically non significant.) At 240 mg/kg orofacial anomalies (cleft palate, cleft lip and open eyelids) were twice that of vehicle controls.
4. Treatment on Days 13 and 14 (240 mg/kg only) caused similar results as that on days 12 and 13, i.e., decreased live births, increased resorptions, and increased cleft palate formation.

In most instances, cleft palate was also accompanied by cleft lip which, in turn, did not vary with treatment.

5. Administration of Delta-9-THC did not effect weights of fetuses.
6. Twenty-Four hours food deprivation on Day 11 of gestation did not adversely affect resorption frequency and developmental abnormalities.

III. Rabbit

Teratogenic Study with Delta-9-THC in Albino Rabbits

Site: Industrial Bio-Test Laboratories, Inc.
1810 Frontage Road
Northbrook, IL 60062

Study No. and Date: IBT No. J335B, 9/21/72, Contract No. HSM-42-71-106.

Species/Strain: New Zealand Albino Rabbits

No. of pregnant rabbits/treatment: 11-18.

Route: Oral (capsule)

Dosage regimen:

<u>Group</u>	<u>Drug</u>	<u>Dose Levels ng/kg</u>	<u># Females Inseminated</u>	<u># Females Pregnant</u>
1	None	--	15	12
2	None	--	20	18
3	Thalidomide	37.5	15	11
4	Delta-9-THC	0.5	20	15
5	Delta-9-THC	1.5	19	17
6	Delta-9-THC	5.0	19	15
7	Delta-9-THC	15.0	20	14

Duration: Day 6-18 of gestation with sacrifice on Day 29.

Results:

1. High dose (15 mg/kg) does showed slight sedation after dosing. This was less apparent at lower dose levels.
2. All treated and control animals survived the study.
3. Fetal survival, as indicated by the number of live young per 100 implantation sites, was slightly reduced in the 5.0 and 15.0 mg/kg groups (91.5 and 75.1 for the two control groups and 83.7, 90.5, 72.2 and 78.2 for the 0.5, 1.5, 5.0 and 15.0 mg/kg groups respectively, 52.0 for Thalidomide positive control).
4. Three fetuses from two 15.0 mg/kg does showed external abnormalities. One fetus had bilateral talipomanus and another had unilateral talipomanus. The third fetus had multiple anomalies such as spina bifida, bilateral talipomanus, unicorn, and acrania.
5. Pup weights were not affected by drug treatment.

6. Dissection of pups delivered by treated females revealed no gross internal abnormalities.

Evaluation and Conclusions

Acute Toxicity Studies, p.o. and i.v. of Delta-9, Delta-8-THC and Crude Marijuana Extract (CME) (p.o. only) in rats, dogs and monkeys; subchronic toxicity studies of Delta-9-THC, p.o. in rats (5, 28, and 90 days), of Delta-8- and Delta-9-THC, p.o. in monkeys (7 days); chronic toxicity studies of Delta-8- and Delta-9-THC, and CME, p.o. in rats (119 days for all three compounds and 180 days for Delta-9-THC), and reproduction studies which included teratology studies in rat, mice and rabbits. In addition, acute cytogenetic studies and hormonal investigations were performed in rats.

Acute toxicity studies, p.o. done in rats for Delta-8-, Delta-9-THC and CME indicated that the three compounds produced similar patterns of toxicity. Treated animals exhibited wide stance, inactivity, hypersensitivity to touch, backward circling, ataxia, hypothermia, hypopnea and weight loss. All pharmacotoxic signs observed indicated a general pattern of CNS depression upon acute administration. Furthermore, as the dose increased, the onset of initial behavioral changes decreased, the duration of effects increased and the developmental sequence of behavioral observations extended. The majority of deceased rats succumbed within 36-72 hours after treatment. These mortality data along with the similar pattern of toxicity suggested that the three compounds exerted their pharmacological effects through similar mechanisms.

I.V. administration of Delta-9- and Delta-8-THC produced essentially similar signs of toxicity as those seen in the oral route of administration except that the pharmacotoxic signs progressed more rapidly, popcorn convulsions occurred more frequently and that almost all deceased rats died within 6 minutes after treatment. Deaths were due to respiratory failure. No hypothermia and inanition were observed in these animals.

Comparison of the three compounds revealed that Delta-9-THC was either more potent than or equi-potent to Delta-8-THC while Delta-9- and Delta-8-THC were much more potent than CME. Sex differences in toxicity were evidenced in both Fischer and Wistar-Lewis rats. The females were found to be more sensitive (approximately 1.5-2.0 times) to the compounds than the males. Strain differences were also apparent. Wistar-Lewis was found to be more susceptible to Delta-9-THC than Fischer rats.

Acute toxicity studies (p.o.) performed in monkeys showed that the three cannabinoids produced similar behavioral changes which included initial hyperactivity, hypersensitivity, followed by lethargy, drowsiness, sedation, hypothermia and ataxia. No death occurred in monkeys administered orally Delta-8- or Delta-9-THC at doses ranging from 131.1-3150 mg/kg and CME at

5000 mg/kg. The I.V. route produced aggressiveness, prostration, convulsions and death in addition to those signs seen in the oral toxicity study. The I.V. LD₅₀ value for Delta-9-THC was approximately 15 mg/kg.

Similar to the monkey studies, acute oral administration of Delta-9-THC at doses of 65.6-3000 mg/kg and Delta-8-THC, 65.6-525 mg/kg, in dogs produced no lethality in these animals. The one dog that died of CME 5000 mg/kg was due to aspiration of the compound. Toxic signs observed in dogs were similar to that obtained in the monkey studies (both p.o. and i.v.). However, as compared to monkeys, dogs appeared to be more sensitive to the three cannabinoids. All deceased animals including monkeys and dogs showed extensive pulmonary hemorrhage and edema upon necropsy. This similarity in histopathology finding after i.v. and p.o. indicated a possibly similar mechanism of death in these animals, i.e., histamine shock. Histamine shock could arise from either local irritation or systemic stresses, aspiration of compound in case of oral administration, and precipitation of Delta-9-THC in case of i.v. route, which in turn caused filtration and blockage in pulmonary capillary bed (the first major capillary bed exposed via i.v. route), local hypoxia, hypotension, histamine release, and finally hemorrhage and edema of the lung. Again, as seen in the rat studies, the potency of the three compounds were in the order of Delta-9-THC greater than or equal to Delta-8-THC which was much greater than CME.

It was clear from these acute studies that absorption posed a significant problem in the oral administration of these cannabinoids and that it also determined, to a certain degree, the extent to which pharmacological effects were to be obtained. The p.o./i.v. dose ratio of Delta-9-THC for rats, monkeys, and dogs appeared to be roughly in the order of 40-60X. Absorption problems along with the species differences in susceptibility to these compounds could easily account for the differences in toxicity observed in these animals.

Subacute studies (5 days, p.o.) done in rats for Delta-9-, Delta-8-THC (both 62.5-1000 mg/kg), and CME (187.5-3000 mg/kg) showed that the pharmacotoxic signs seen for these three compounds were essentially similar to that observed in acute studies for this species. A dose of 250 mg/kg for Delta-9- and Delta-8-THC, and 750 mg/kg for CME was found to be well tolerated in these animals. Again, mortality was due to CNS depression. However, an important pharmacological sign did emerge from these five-day studies. Tolerance was evidenced either by decreased severity of effects or increased rate of recovery. Tolerance was found to develop on the third day of the treatment and was inversely dose related. Pathological findings obtained in these studies indicated the involvement of bone marrow and spleen, i.e., hypocellularity of bone marrow and germinal center atrophy of the spleen (Delta-9- and Delta-8-THC, above 500 mg/kg; CME, above 750 mg/kg). For Delta-8-THC, additional pathological findings were observed, they were degeneration of seminiferous tubules and necrosis and mineralization of

adrenal cortex. Weight gain depression occurred in the acute studies (p.o.) was found to persist in the five-day studies. Organ weight changes included increases in adrenal and liver weights and a decrease in spleen weight.

Seven-day study (p.o.) carried out in monkeys for Delta-9- and Delta-8-THC (both up to 5 gm/kg) also indicated the emergence of tolerance in this species. Pharmacotoxic signs other than those seen in rats were persistent anorexia and temporary constipation. Similar to the rat studies, bone marrow hypocellularity was observed. Drug absorption seemed to present even a greater problem in this species than in the rats since no further increases in pharmacological effects were observed as dose of Delta-8- and Delta-9-THC was increased up to 5 gm/kg/day. No mortality occurred at this high dose level. Clearly tolerance could only account for part of the observations obtained.

Subchronic and chronic studies done in rats (Delta-9-THC, 2-500 mg/kg; Delta-8-THC, 50-500 mg/kg; and CME, 150-1500 mg/kg) showed that the three cannabinoids displayed qualitatively similar signs of toxicity. The general pattern was a biphasic one, i.e., initial CNS depression including hypothermia, hypopnea, inactivity, drowsiness, sedation, wide stance, hypersensitivity to touch, ataxia and weight gain depression to which tolerance developed in the first week or so, thereafter the central depression was replaced by CNS stimulation as evidenced by hyperactivity, irritability, development of fighting behavior, tremor and convulsion. Fighting behavior occurred in cyclic fashion and was inversely dose related. Tremor and convulsion occurred at high dose level and was dose and treatment duration related. Tolerance to convulsion was not seen. The weight gain depression was persistently seen throughout the chronic studies and was initially associated with a normal or slightly decreased food intake. Hypopnea lasted for up to 4 months of drug administration, thereafter the degree of hypopnea decreased. Hypocellularity of bone marrow and spleen as well as necrosis and vacuolization of the adrenal cortex were found in rats treated subchronically and chronically with high levels of these cannabinoids (Delta-9- and Delta-8-THC, above 250 mg/kg; CME, above 400 mg/kg). No such pathological changes were observed with Delta-9-THC at doses below 50 mg/kg. For Delta-8-THC and CME, additional pathological changes; degeneration of seminiferous tubules occurred. The hypocellularity seen in the bone marrow and spleen might be related to the immunosuppressive responses reported for these cannabinoids. Organ weight changes included a consistent increase in adrenal weight and a decrease in pancreas, pituitary and uterus weight in general. Clinical chemistry revealed elevations in serum SGOT, SGPT, glucose, hematocrit and red blood cell count in the Delta-9-THC treated animals. The significance of these changes is not clear since no concomitant pathological findings were observed.

Reproduction studies done in rats, mice and rabbits indicated a general agreement that Delta-9-THC was not teratogenic. In A/J mice, although Delta-9-THC (240 mg/kg) was shown to increase orofacial anomalies (cleft

palate, cleft lips and open eyelids), it did not induce new type(s) of fetal anomalies. Delta-9-THC, however, did possess fetal toxicity which included a decrease in number of viable pups, increase in fetal mortality, and increase in early resorption (12.5-50 mg/kg in rats, 50-600 mg/kg in mice). Maternal parameters such as body weights of dams, pregnancy rate, and uterine weights were also affected (decreased). Hormonal investigations showed that there were changes in serum FSH, LH, estrogen and progesterone but no consistent pattern could be discerned. The observed fetal toxicity might be related to the hormonal swing seen in these animals. In male rats, Delta-9-THC (5-25 mg/kg) caused a decrease in ventral prostate weights, epididymal weights, seminal vesicle weights and seminal fluid volume. At 25 mg/kg, it produced areas of sparse Leydig cells in the interstitium of testis, also a decrease in spermatogenesis and in number of developing germ cells in the seminiferous tubules. It did not, however, affect sperm count, serum testosterone, mating success and offspring weight. It appeared sufficient area of normal Leydig cells population remained to allow for production of normal level of testosterone and for performance of normal reproduction function.

Acute cytogenic studies done in bone marrow of Sprague-Dawley rats indicated that Delta-9-THC (50 mg/kg) caused no significant changes in the frequency of chromosome aberration and mitotic index, nor did Delta-9-THC (0.2 and 1 mg/plate) result in any significant change in the reversion rates of S. typhimurium. No carcinogenicity studies were submitted.

RECOMMENDATIONS:

Pharmacologically the NDA is approvable for the indication proposed, i.e., anti-nauseant in cancer patients receiving chemotherapy. The possible benefits of Delta-9-THC in such patient population outweigh its risk.

Geraline C. Lin, Ph. D.

Geraline C. Lin, 2/15/84



Chem. Rev

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

NDA/ 18-651

Review of Chemistry and Manufacturing Controls

Applicant: UNIMED, INC.
Sponsor: 35 Columbia Road
Address: Somerville, N. J. 08876

Division: HFD-120
Chemist Review # 2
Reviewing Chemist: S.W. Blum, Ph.D.

Date Completed: 2/10/84

Product Name(s):

Proprietary: MARINOL
Non proprietary: delta-9-tetrahydrocannabinol
Compendium:
USAN:
Code name/number:

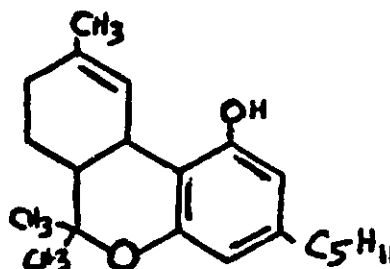
Dosage Form(s) and Route(s) of Administration: Capsules (2.5, 5, 10 mg)

Pharmacological Category and/or Principal Indication: Antinauseant (adjunctive)

Structural Formula & Chemical Name:

delta-9-tetrahydrocannabinol

6aR-trans-6a,7,8,10a-tetrahydro-
6,6,9-trimethyl-3-pentyl-6H-
dibenzo b,d pyran-1-ol



Initial Submission: RS 9/24/82
Amendment(s): 2/22/83; 4/8/83; 7/6/83; 8/31/83; 11/1/83
Related Documents:

Remarks:

Responses to all deficiencies per FDA 12/6/82 letters to Unimed [redacted] - this was the 2/22/83 AM.
Inspection report from HFN-322 (11/8/83) is satisfactory -- attached.
Application amended (4a,8h,8i, in 2/22/83 AM) -- information adequate. Use of 24-month expiration date acceptable.
Methods validation [redacted]

Conclusions and Recommendations:

All deficiencies of FDA 12/6/82 letter corrected. EIR satisfactory. Added package (bottle of 50) and use of 24-month expiry satisfactory. Methods validation pending [redacted]

Recommend APPROVABLE. Draft portion of SBA attached [redacted]

Stanley W. Blum, Ph.D.
S. W. Blum, Ph.D.

mor

Review and Evaluation of Clinical Data
NDA 18-651

JUN 10 1984

Applicant: Unimed, Inc.

Drug: Marinol (delta-9-tetrahydrocannabinol; D-9-THC)

Date submitted: June 24, 1981

Date reviewed: November 15, 1983

Medical Officer's Review of Safety and Efficacy Data Submitted in Support of the Approval of Marinol as Antiemetic Agent in Patients Receiving Cancer Chemotherapy.

Background:

While recent advances in chemotherapeutic regimens have helped prolong life in many instances, the side effects of these drugs often are intolerable to patients. This may result in the premature discontinuation of these drugs, with resultant shortening of life. Therefore, the search for more and better antiemetics to use in this setting is quite active. However, studying these antiemetics is not always a straightforward and simple undertaking.

One of the more difficult problems encountered in the study of these agents is the construction of meaningful rating scales to assess their efficacy. This is particularly problematic in dealing with nausea, as this is an entirely subjective sensation. While most studies apply numerical ratings to varying degrees of nausea, this can often give an appearance of objectivity to a study where none really exists. Since these ratings are usually (if not always) decided by the patients themselves, the question of inter-rater reliability must always be kept in mind. Usually, these scales are most meaningful only at the extreme ratings (i.e., no nausea or severe, incapacitating nausea). It is at these points that there is the least doubt about their validity.

The problem of assessing the effects of an antiemetic on the occurrence of vomiting is less subject to error though it is not necessarily clear-cut. The occurrence of vomiting (or retching) is easier for patient and rater to acknowledge - it either happens or it doesn't. Many studies arbitrarily divide number of episodes of vomiting into "success" categories. This is, for instance, less than 5 episodes/24 hours is a "good" response, etc. These scales, too, are most meaningful at the end-points; either no vomiting, or incapacitating vomiting (or some reasonable equivalent.) Other studies attempt to document the amount of emesis produced in a given time period. Not only is this difficult to collect in its entirety, but is dependent on a

number of difficult to control for factors, such as food intake. This makes this parameter difficult to rely on. Finally, as with nausea, since many studies are in outpatients, the question of accurate, reliable documentation is often a real one.

A very real problem in most studies of antiemetic efficacy in this population is the standardization of the chemotherapy. Almost all large studies enroll patients on multiple, different chemotherapy regimes. Since it is well accepted that different anti-cancer drugs have different emetogenic potential (although people can not always agree on what this is for a given drug) it may be difficult to come to a meaningful conclusion about an antiemetic's potential to decrease (or prevent) nausea and vomiting caused by a specific agent. Studies, therefore, that look at the responses of patients who are all taking the same chemotherapy will be the easiest to interpret. The other studies, however, can be interpreted meaningfully as well, if an effect of drug can be shown to hold up (as compared with placebo, ideally) in randomly assigned patients, with all chemotherapy regimens represented in both active and control groups.

Another problem associated with chemotherapy is anticipatory vomiting (or nausea), which is the occurrence of symptoms in anticipation of the chemotherapy, in patients who have received chemotherapy in the past. This is a conditioned response, and may actually occur upon seeing the hospital, approaching a ward, etc. It can result in symptoms before receiving the chemotherapy, and may last after the drug is given, thereby interfering with the assessment of the "true" emetogenic potential of the drug. Since it is possible that anticipatory nausea and vomiting occur via a separate mechanism than direct chemotherapy-induced nausea and vomiting, one might not expect them to respond in the same way to a given antiemetic. This may make the results of such a study questionable. In a randomized study, though, patients with anticipatory symptoms should be evenly distributed among the treatment groups. Also, studying only patients who are starting chemotherapy should minimize this effect. Recording baseline nausea and vomiting data, though rarely done, might also be helpful in this regard.

THC studies have, in addition, some more specific problems. Prior marijuana use may be a factor in a patient's response to chemotherapy. This point remains controversial. Also there is a sense that older patients have a more difficult time dealing with the psychological symptoms caused by THC, and this confounds the results, as does pre-study attitude towards marijuana.

Most (if not all) of the studies submitted in this NDA fall victim to one or a number of the problems discussed above (as well as to a number of more general methodologic problems). Different rating scales are used in many of the studies, arbitrary end points determined, multiple chemotherapy regimens are employed, prior marijuana use and age are not specifically looked at, baseline measures are rare, and placebo is not universally employed. Still, meaningful data has been generated, and efficacy can be demonstrated.

STUDY

This was a two-part study. Part I involved patients treated only with methotrexate. Part II included patients on a regimen of Adriamycin and Cytosan. Only Part I will be discussed now. Part II will be detailed later in this review.

Part I was a single, blind, placebo-controlled, crossover, randomized study comparing the antiemetic and anti-nauseant effects of THC to placebo in patients with osteogenic sarcoma receiving Methotrexate.

Fifteen (15) patients were entered into the trial, which was broken into two phases. In Phase I, patients received 6 courses of antiemetic treatment, corresponding to 6 courses of I.V. Methotrexate, 250 mg/kg I.V. given over 6 hours. Patients were randomized to either THC-placebo or placebo-THC treatment plans.

Patients

Fifteen (15) patients aged 15-49 years, with median age of 24. All had osteogenic sarcoma; all had had surgical removal of their tumors. Four (4) of the patients had not used marijuana previously.

Dosing

Patients were dosed 2 hours prior to the chemotherapy treatment, and then at 3-hour intervals for a total of 5 doses, and they were evaluated every waking hour during a 24-hour period. Treatments were given 3 weeks apart. The dose was 10 mg/M² (each dose).

Efficacy variables: The efficacy variables were as follows:

1. Total number of vomiting and retching episodes - This represented the total number of times vomiting (defined as 30 ml of emesis) and retching occurred in a 24-hour period.

2. Total volume of emesis - This was the quantity of vomitus in that 24-hour period.

3. Total degree of Nausea - This was rated hourly according to the following scale:

- 0 - None
- 1 - Slightly
- 2 - Moderate
- 3 - Greatly

The sum of these hourly scores is the total degree of nausea.

4. Total Duration of Nausea - The total amount of time during the wakeful state was measured.

5. Investigator's Assessment - A global assessment by the investigator was made according to the following criteria:

Excellent - > 80% reduction for all 4 variables compared to placebo.

Fair - 30% but < 80% reduction of at least 2 variables.

No response difference - < 30% reduction of at least 2 variables.

6. Applicant's Assessment of THC Response - The applicant rated THC compared to placebo according to the following classifications:

Excellent - >80% reduction for all 4 variables compared to placebo.

Partial - >50% but < 80% reduction of nausea or vomiting variables.

Poor - <50% reduction of nausea or vomiting and includes any patient who substituted a THC cigarette for any capsule dose.

Results - First, I will discuss the adverse reactions noted.

Six (6) patients had dysphoric reactions while on THC. None had a dysphoric reaction while taking placebo. Five of the six were disoriented, and felt as if they were being controlled by an outside force. All continued the study. Each reaction occurred after the initial A.M. THC dose, and lasted 20-45 minutes. No specific therapy was required.

All 15 patients experienced a "high" while on THC; 12/15 were drowsy while on placebo, and 2/15 experienced a "high" while on placebo. 7/15 patients had a tachycardia while on THC. Several patients felt anxious and depressed while on placebo.

Efficacy - All 15 patients in Phase I completed both treatment periods of the first paired trial and were included in the analyses.

The results of an analysis by Koch method revealed no effect on efficacy variables measured of either sequence of antiemetic treatment or treatment period. That is, differences noted in these variables were solely related to treatment.

When totals of all 4 variables (summed over all paired trials) (10 patients had 3 trials, 2 had 2 trials, and 3 had 1 paired trial), 9/15 patients had an excellent response, and 5/15 had a fair response.

The differences in each of the 4 variables (summed over all paired trials) were significant at the $p < 0.01$ level in favor of THC over placebo.

Comments - Nausea and vomiting caused by cancer chemotherapy is a syndrome that is amenable to a crossover design. The crucial requirement of a condition that allows a crossover design to be utilized are that the study drug does not permanently alter the patient's condition and the condition has a predictable natural history. It is reasonably safe to assume that the use of an antiemetic in one treatment period does not seriously alter the potential (whatever that happens to be) of the same chemotherapy causing nausea and vomiting at a different time (particularly 3 weeks later, as in this study). Here, of course, the possibility of anticipatory nausea can play a role, but this likely had little effect here. Also, the "natural history" of this syndrome is undoubtedly, for the most part, unchanged with time, making it suitable for this study methodology.

There is the problem with blinding, of course, in this study. However, an attempt to design this study as a double-blind would have been merely a pretense; the high incidence of relatively specific THC side effects would have destroyed the blind. This is a problem for which there is no easy solution in these studies.

The high incidence rate of severe side effects is troubling, but not dangerous in my view. Though the drug clearly results in many adverse reactions, they are all temporary and resolved with time and no treatment. It is not terribly surprising that a medication that is required to be potent carries with it a high risk of ADRs. The transient nature of the reactions, though, make their incidence less worrisome.

As regards efficacy, these data are compelling. Not only did 14/15 patients fare better than placebo (according to the Investigator's Assessment - Table 10) but the fact that there was a significant difference in all 4 variables, over all paired trials, between THC and placebo, is strong evidence that the drug is effective as an antiemetic. However, it should be pointed out that summing over all paired trials is not entirely reasonable, as 2 patients only completed 2 trials, and 3 completed only 1 trial, and we are not told the reasons for the dropouts along the way. Still, a look at Tables 6-8, in which the raw data are displayed, confirms that THC had a powerful antiemetic effect. Even if only Table 6 is taken into account (including all 15 patients), we see a strongly active drug.

As can be seen from this raw data, these differences noted are clinically meaningful. The marked decrease in the number of vomiting and retching episodes (a fairly reliable criterion) is striking. Though the other variables are less "objective", a crossover design helps minimize rater differences (as each patient rates him or herself on each medication). These are seen to be positively effected by THC in comparison to placebo.

This study is considered pivotal. It is well designed, with no serious methodological flaws. The efficacy results are statistically significant, and

TABLE 6

PHASE I METHOTREKATE STUDY GROUP

NAUSEA & VOMITING OCCURRENCE DURING 1ST PAIRED ANTIEMETIC TRIAL ACCORDING TO CROSS-OVER SEQUENCE

Pt. No.	Age	Sex	Total No. Vomiting & Retching Episodes		Total Volume Emesis (ml)		Total Degree Nausea		Total Duration of Nausea (min.)		Investigator's Assessment of THC Response *	Applicant's Assessment of THC Response **
			THC	P	THC	P	THC	P	THC	P		
THC 1st Drug												
[REDACTED]	[REDACTED]	[REDACTED]	7	16	390	1165	7	10	37	46	Fair	Poor (THC cig.)
[REDACTED]	[REDACTED]	[REDACTED]	0	0	0	0	0	10	0	195	Excellent	Partial
[REDACTED]	[REDACTED]	[REDACTED]	2	21	75	690	2	22	20	530	Excellent	Poor (THC cig.)
[REDACTED]	[REDACTED]	[REDACTED]	0	21	0	650	3	18	10	270	Excellent	Excellent
[REDACTED]	[REDACTED]	[REDACTED]	0	20	0	905	0	11	0	30	Excellent	Excellent
[REDACTED]	[REDACTED]	[REDACTED]	0	0	0	0	4	0	7	0	No Response	Poor
[REDACTED]	[REDACTED]	[REDACTED]	16	21	650	900	16	26	165	490	Fair	Partial
[REDACTED]	[REDACTED]	[REDACTED]	0	4	0	150	0	17	0	175	Excellent	Excellent
[REDACTED]	[REDACTED]	[REDACTED]	0	0	0	0	7	6	30	0	Fair	Poor
[REDACTED]	[REDACTED]	[REDACTED]	0	5	0	325	0	15	0	71	Excellent	Excellent
Placebo 1st Drug												
[REDACTED]	[REDACTED]	[REDACTED]	36	7	810	325	18	11	230	19	Fair	Poor (THC cig.)
[REDACTED]	[REDACTED]	[REDACTED]	17	0	450	0	11	1	220	0	Excellent	Excellent
[REDACTED]	[REDACTED]	[REDACTED]	3	0	300	0	27	0	510	0	Excellent	Excellent
[REDACTED]	[REDACTED]	[REDACTED]	37	12	1200	1025	20	16	270	200	Fair	Partial
[REDACTED]	[REDACTED]	[REDACTED]	6	11	600	475	12	12	190	30	Fair	Poor

* Investigator's THC response scale:

Excellent = > 80% reduction for all 4 nausea and vomiting variables compared to placebo.

Fair = > 30% but < 80% reduction of at least 2 nausea and vomiting variables.

No Response difference = < 30% reduction of at least 2 nausea and vomiting variables.

** Applicant's THC response scale:

Excellent = > 90% reduction for all 4 nausea and vomiting variables compared to placebo.

Partial = > 50% but < 80% reduction of vomiting or nausea variables.

Poor = < 50% reduction of nausea or vomiting variables, and includes any patient who substituted a THC cigarette for any THC capsule dose.

Patient had no previous marihuana experience.

TABLE 7

PHASE I METHOTREXATE STUDY GROUP

NAUSEA & VOMITING OCCURRENCE DURING 2ND PAIRED ANTIEMETIC TRIAL ACCORDING TO CROSS-OVER SEQUENCE

Pt. No.	Age	Sex	Total No. Vomiting & Retching Episodes		Total Volume Emesis (ml)		Total Degree Nausea		Total Duration of Nausea (min.)		Investigator's Assessment of THC Response *	Applicant's Assessment of THC Response **
			THC	P	THC	P	THC	P	THC	P		
THC 1st Drug			8	7	400	655	8	18	85	120	Fair	Poor (THC cig.)
[REDACTED]			16	14	675	1240	14	21	150	160	Fair	Poor (THC cig.)
[REDACTED]			0	49	0	925	0	16	0	465	Excellent	Excellent
[REDACTED]			0	29	0	650	0	15	0	250	Excellent	Excellent
[REDACTED]			28	48	2275	1530	20	25	45	353	Fair	Poor (THC cig.)
[REDACTED]			0	6	0	400	2	14	10	180	Excellent	Excellent
[REDACTED]			0	6	0	400	0	12	0	125	Excellent	Excellent
Placebo 1st Drug			10	3	740	145	33	5	663	60	Excellent	Excellent
[REDACTED]			5	1	1000	50	6	0	25	0	Excellent	Excellent
[REDACTED]			0	0	0	0	0	0	0	0	No Response	Poor
[REDACTED]			40	6	970	450	18	6	290	20	Excellent	Excellent
[REDACTED]			13	0	650	0	15	0	150	0	Excellent	Excellent

* Investigator's THC response scale:

- Excellent = > 80% reduction for all 4 nausea and vomiting variables compared to placebo.
- Fair = > 30% but < 80% reduction of at least 2 nausea and vomiting variables.
- No Response difference = < 30% reduction of at least 2 nausea and vomiting variables.

** Applicant's THC response scale:

- Excellent = > 80% reduction for all 4 nausea and vomiting variables compared to placebo.
- Partial = > 50% but < 80% reduction of vomiting or nausea variables.
- Poor = < 50% reduction of nausea or vomiting variables, and includes any patient who substituted a THC cigarette for any THC capsule dose.

Patient had no previous marijuana experience.

TABLE 8

PHASE I METHOTREXATE STUDY GROUP

NAUSEA & VOMITING OCCURENCE DURING 3RD PAIRED ANTIEMETIC TRIAL ACCORDING TO CROSS-OVER SEQUENCE

Pt. No.	Age	Sex	Total No. Vomiting & Retching Episodes		Total Volume Emesis (ml)		Total Degree Nausea		Total Duration of Nausea (min.)		Investigator's Assessment of THC Response *	Applicant's Assessment of THC Response **
			THC	P	THC	P	THC	P	THC	P		
THC 1st Drug												
			1	ND	50	ND	6	ND	36+	ND	Not Evaluable	Not Evaluable
			1	18	50	690	3	22	50	395	Excellent	Excellent
			9	22	650	1365	10	18	30	127	Excellent	Excellent
			0	3	0	300	0	14	0	170	Excellent	Excellent
Placebo 1st Drug												
			27	ND	1160	ND	25	ND	265	ND	Not Evaluable	Not Evaluable
			33	0	425	0	13	0	120	0	Excellent	Excellent
			29	1	1720	500	13	2	165	0	Excellent	Excellent
			27	8	700	450	16	5	127	35	Excellent	Poor (THC cig.)
			0	0	0	0	0	0	0	0	No Response	Poor
			30	13	775	900	23	8	191	120	Fair	Poor (THC cig.)
			7	3	350	450	8	1	85	10	Excellent	Excellent
			8	0	580	0	14	0	105	0	Excellent	Excellent

* Investigator's THC response scale:

Excellent = > 80% reduction for all 4 nausea and vomiting variables compared to placebo.

Fair = > 30% but < 80% reduction of at least 2 nausea and vomiting variables.

No Response difference = < 30% reduction of at least 2 nausea and vomiting variables.

** Applicant's THC response scale:

Excellent = > 80% reduction for all 4 nausea and vomiting variables compared to placebo.

Partial = > 50% but < 80% reduction of vomiting or nausea variables.

Poor = < 50% reduction of nausea or vomiting variables, and includes any patient who substituted a THC cigarette for any THC capsule dose.

Patient had no previous marijuana experience.

TABLE 10

**SUMMARY OF NAUSEA & VOMITING EPISODES
IN PATIENTS RECEIVING METHOTREXATE**

Phase I

Patient	No. of Paired Trials	Total No. Vomiting & Retching Episodes		Total Volume of Emesis (ml)		Total Degrees of Nausea		Total Duration of Nausea (min)		Response to THC
		THC	P	THC	P	THC	P	THC	P	
[REDACTED]	2	15	23	790	1820	15	26	122	166	Fair
[REDACTED]	2	23	50	1000	2050	25	40	169	390	Fair
[REDACTED]	1	0	0	0	0	0	10	0	195	Excellent
[REDACTED]	3	0	99	0	1800	1	40	0	805	Excellent
[REDACTED]	3	4	31	195	1730	8	82	110	1568	Excellent
[REDACTED]	1	2	21	75	690	2	22	20	530	Excellent
[REDACTED]	3	1	79	500	3020	5	46	10	650	Excellent
[REDACTED]	3	49	108	5950	4095	46	63	275	750	Fair
[REDACTED]	3	9	52	500	2605	5	33	35	182	Excellent
[REDACTED]	3	0	0	0	0	4	0	7	0	No Response
[REDACTED]	3	35	91	2000	2645	30	67	305	971	Fair
[REDACTED]	3	14	26	925	1600	13	35	40	425	Fair
[REDACTED]	3	0	18	0	1130	2	45	10	460	Excellent
[REDACTED]	3	0	9	0	700	7	32	30	295	Excellent
[REDACTED]	1	0	5	0	325	0	15	0	71	Excellent

TABLE 11

WILCOXON SIGNED-RANKS ANALYSIS OF NAUSEA AND VOMITING
VARIABLES SUMMED OVER ALL PAIRED TRIALS

Chemotherapy Treatment	Variable	Wilcoxon Analysis		
		N	T	Significance Level
Methotrexate	Total Episodes - Vomiting & Retching	13 ^a	0	P < 0.01
	Total Volume Emesis	13 ^a	0	P < 0.01
	Total Degrees of Nausea	15	1	P < 0.01
	Total Duration of Nausea (min.)	15	1	P < 0.01
Adriamycin/ Cytosin	Total Episodes - Vomiting & Retching	8	20	P > 0.05
	Total Volume Emesis (ml)	8 ^b	7	P > 0.05
	Total Degrees of Nausea	7 ^b	18	P > 0.05
	Total Duration of Nausea (min.)	8	20	P > 0.05
Combined	Total Episodes - Vomiting & Retching	21	30.5	P < 0.01
	Total Volume Emesis (ml)	21	39	P < 0.01
	Total Degrees of Nausea	22	19	P < 0.01
	Total Duration of Nausea (min.)	23	29	P < 0.01

^a Two patients on Methotrexate had a difference between placebo and THC equal to zero, and are excluded from the analysis.

^b One patient on Adriamycin/Cytosin exhibited a difference between placebo and THC of zero, and is excluded from analysis.

TABLE 12SUMMARY OF SIGN TEST
FOR INVESTIGATOR AND APPLICANT
OVERALL ASSESSMENTS

Chemotherapy Treatment	Assessment Variable	THC Better*	THC Not Better	Binomial P-Value
Methotrexate	Investigator	14	1	0.001
	Applicant	9	6	0.60
Adriamycin/ Cytosan	Investigator	3	5	0.72
	Applicant	1	7	0.07
Combined	Investigator	17	6	0.034
	Applicant	10	13	0.68

* For Investigator: Excellent or fair rating, all paired trials.
For Applicant: Excellent or partial rating, first paired trial.

more importantly, clinically significant. The large incidence of side effects is, obviously, undesirable, but do not stand in the way of making a positive risk/benefit judgment in favor of THC over placebo on the basis of this study. Though the numbers are small, this study is considered positive.

KLUIN-NELEMANS STUDY

This was a double-blind, placebo-controlled crossover design study in patients receiving MOPP therapy for Hodgkin's and non-Hodgkin's lymphoma. These patients were, for the most part, found to have been previously refractory to standard antiemetic therapy.

Patients - Eleven patients entered the trial, but only 9 completed their study, 2 having dropped out after receiving THC. There were 10 men and 1 woman, the ages ranged from 20-53, with the mean age 34.6 years.

Drug Schedules and Dosages - MOPP therapy was given in a 14-day cycle, in the following manner:

On days 1 and 8 patients received an I.V. infusion of chlormethine (6 mg/M², maximum 10 mg) and vincristine (1.4 mg/M², maximum 2 mg). In addition, patients received daily for 14 days oral procarbazine, 100 mg/M² and prednisone, 40 mg/M². Each patient received 6 cycles of MOPP.

Patients were randomly assigned to one of 4 sequence groups of THC- placebo treatment, consisting of 3 chemotherapy cycles each. During each cycle, patients were given antiemetic treatment on days 1 and 8. The antiemetic was given 2 hours prior to chemotherapy and then at 4 and 8 hours later. The dose of THC was 10 mg/M².

Efficacy Variables - Three efficacy variables were looked at:

A. Occurrence of Nausea

1. None
2. Mild, activity not interfered with
3. Moderate, activity interfered with
4. Severe; bedridden for more than 2 hours.

B. Occurrence of Vomiting

1. No vomiting 24 hours after chemotherapy

2. Mild, vomiting less than 5 times in 24 hours
3. Moderate, vomiting 5-10 times
4. Severe, 10 times, bedridden.

C. Overall Response

Complete response - no nausea and vomiting

Partial response - 2 or 3 nausea and vomiting and at least 50% reduction of nausea and vomiting in patients previously refractory to standard antiemetics.

No response - Grade 4 nausea and vomiting, or less than 50% reduction of nausea and vomiting in previously refractory patients.

Analysis - The data used for analysis consisted of the first THC and first placebo treatment for each patient. This created a 2-period crossover design to which the method of Koch was applied. Scores from day 1 and day 8 from each antiemetic treatment group were summed for the analysis. The statistic calculated was the Mann-Whitney U Statistic.

Observations - The patient was observed every half hour. The patient was questioned at the end of the day about the occurrence of nausea and vomiting, and compared the effect of the first day of the trial and previous pre-treatment first cycle days. This was also done for day 8.

Results - Adverse Reactions -

10/11 patients (91%) experienced a "high" on THC; 6/11 experienced dysphoric reactions, including fear and anxiety (5 patients), time distortions (4 patients), hallucinations (3 patients), depersonalization and mania. Two (2) patients discontinued the study due to dysphoric reactions.

9/11 (82%) patients were somnolent on THC, and 11/11 (100%) experienced dizziness. Other, less frequent side effects on THC were ataxia (27%), parasthesiae (27%) and headache (27%).

Side effects on placebo were rare. One of 9 (11%) had difficulty in concentrating, and 2/9 (22%) experienced a headache.

Efficacy - Five (5) patients were treated in the THC-placebo sequence and 4 in the placebo-THC sequence.

Nausea - Total nausea scores on THC were 43 (adding days 1 and 8) and 69 on placebo; means were 2.4 and 3.8 respectively. This difference was determined to be statistically significant.

Vomiting - Total vomiting scores on THC and placebo respectively were 36 and 69, with means of 2.0 and 3.8 respectively. This, too, was statistically significant.

Overall Response - Total overall response on THC and placebo were 37 and 20, with means of 2.1 and 1.1, a statistically significant difference.

Table 8 shows that scores were significantly related only to treatment and not to period or sequence effects.

Comments -

Once again, a high incidence of adverse reactions was noted in the THC portion of the study. These reactions were all self-limited, requiring no specific therapy. Their rate of occurrence is troublesome, as is their character, yet they do not overshadow or negate the demonstrated efficacy of THC as an anti-nauseant.

The analyses show that each variable measured was significantly positively effected by THC as compared to placebo. (Previous comments have been made about the suitability of a crossover design in this study). I would defend the maneuver of looking only at days 1 and 8 of a cycle, because those were the days of maximum emetogenic stimulus.

One point that we can look at is the apparent arbitrariness of, in particular, the vomiting rating scale. Grades 2 and 3 appear, perhaps, to be somewhat arbitrarily divided, and might be more meaningful if combined. With this in mind, these totals and means were re-calculated changing a score of 2 to a score of 3.

<u>Totals</u>	<u>THC</u>	<u>PLACEBO</u>
Nausea	49	69
Vomiting	40	70
<u>Means</u>	<u>THC</u>	<u>PLACEBO</u>
Nausea	2.7	3.8
Vomiting	2.2	3.8

Even when this transformation is performed, a significant difference is maintained.

These differences, in my view, clearly reflect clinically meaningful responses to THC as compared to placebo. Patients on placebo were essentially bedridden with both nausea and vomiting. It has been demonstrated, particularly with vomiting (a more "reliably" measured parameter), that patients were much better able to tolerate their chemotherapy while on THC. While nausea and vomiting were not, on the average, obliterated, they were held in check.

**CHRONOLOGY OF NAUSEA SCORES
ACCORDING TO DRUG SEQUENCE**

00432

Pt. #	Initials	Age	Sex	1st Chemo Cycle			2nd Chemo Cycle			3rd Chemo Cycle			Sum of Day 1 and 8 Scores for Data Utilized in Crossover Analysis			
				Nausea Score Response		Nausea Score Response		Nausea Score Response		Nausea Score Response		Nausea Score Response		TREATMENT	THC	P
				Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8			
THC-Placebo-THC Sequence				THC ^a	Placebo ^a	Placebo ^a	THC	THC	Placebo	THC	6	8				
				3	3	4	4	2	1	2	1	3	8			
				2	1	4	4	2	1	2	1	2	8			
				4	3	4	4	4	4	4	4	7	8			
				4	3	4	4	4	4	Not Done	Not Done	7	8			
Placebo-THC-Placebo Sequence				Placebo ^a	THC ^a	THC ^a	Placebo	Placebo	Placebo	Placebo	5	8				
				4	4	3	2	4	3	4	3	3	8			
				4	4	2	1	2	4	*2	4	3	8			
				4	4	4	1	4	3	4	3	5	8			
THC-THC-Placebo Sequence				THC ^a	THC ^a	THC ^a	Placebo	Placebo	Placebo	Placebo	4	5				
				2	2	2	1	4	1	4	1	3	8			
Placebo-THC-THC Sequence				Placebo ^a	THC ^a	THC ^a	THC	THC	THC	THC	3	8				
				4	4	2	1	2	1	2	1	3	8			
THC-No Cross-Over				THC	THC	THC	THC	THC	THC	THC	43	69				
				3	Not Done	3	Not Done	3	Not Done	3	Not Done	2.4	3.8			
				2	2	2	2	2	2	2	2	Totals				
				* THC taken instead of placebo								Mean b				

b Mean Score: Total : (2x9)

SCORE: 1 - Grade I
2 - Grade II
3 - Grade III
4 - Grade IV
a - Utilized in cross-over analysis

TABLE 6

CHRONOLOGY OF OVERALL RESPONSE SCORES
ACCORDING TO DRUG SEQUENCE

Pt. #	Patient Initials	Age	Sex	1st Chemo Cycle		2nd Chemo Cycle		3rd Chemo Cycle		Sum of Day 1 and 8 Scores for Data Utilized in Crossover Analysis	
				Nausea & Vomiting Response Day 1 Course	Day 8 Course	Nausea & Vomiting Response Day 1 Course	Day 8 Course	Nausea & Vomiting Response Day 1 Course	Day 8 Course	T	H
TUC-Placebo-THC Sequence											
				THC ^a		Placebo ^a		Placebo ^a		THC	
				1	2	1	1	2	3	3	2
				2	3	1	1	2	3	5	2
				1	2	1	1	1	1	3	2
				1	3	1	2	Not Done		4	3
Placebo-THC-Placebo Sequence											
				Placebo ^a		THC ^a		Placebo			
				1	1	2	2	1	2	4	2
				1	1	2	3	1	1	5	2
				1	1	2	2	2	2	4	2
TUC-THC-Placebo Sequence											
				THC ^a		Placebo ^a		Placebo ^a			
				2	2	2	2	1	2	4	3
Placebo-THC-TUC Sequence											
				Placebo ^a		THC ^a		THC			
				1	1	2	3	2	3		
TUC - No Cross-Over											
				THC							
				2	Not Done						
				2	2						
				Mean b							
										Totals	37 20
											2.1 1.1

00434

SCORE: 3 - Complete Response - No vomiting, no nausea
 2 - Partial Response - Mild or moderate vomiting or nausea
 1 - No Response - Severe vomiting or nausea
 a - Utilized in cross-over analysis
 b Mean Score: Total ÷ (2x9)

**SUMMARY OF ANTIEMETIC RESPONSES
ACCORDING TO NAUSEA AND VOMITING GRADES**

Patient #	Patient Initials	Placebo Response Day 1			THC Response Day 1			Placebo Response Day 8			THC Response Day 8			Previous Antiemetic Response						
		Nausea Grade	Vomiting Grade	Overall Response	Nausea Grade	Vomiting Grade	Overall Response	Nausea Grade	Vomiting Grade	Overall Response	Nausea Grade	Vomiting Grade	Overall Response	Nausea Grade	Vomiting Grade	Overall Response	Drug *	Nausea Grade	Vomiting Grade	Overall Response
		IV	IV	None	III	III	Partial	IV	IV	None	III	I	I	Partial	IV	1)PCZ 2)TEP	IV	IV	None	
		IV	IV	None	II	II	Partial	IV	IV	None	I	I	Complete	IV	None		IV	IV	None	
		IV	IV	None	III	III	Partial	IV	IV	None	II	I	I	Complete	IV	1)PCZ 2)TEP	IV	IV	None	
		IV	IV	None	II	II	Partial	I	II	Partial	II	I	I	Partial	PCZ		III	III	Partial	
		IV	IV	None	II	II	Partial	IV	IV	None	I	I	Complete	IV	1)PCZ 2)TEP		IV	IV	None	
		--	--	--	III	III	Partial	--	--	--	--	--	--	--	PCZ		IV	IV	None	
		IV	IV	None	IV	IV	None	IV	IV	None	I	I	Complete	IV	1)TEP 2)MCP		IV	III	None	
		IV	IV	None	II	II	Partial	IV	IV	None	II	I	I	Complete	None		III	IV	Partial	
		--	--	--	II	I	Partial	--	--	--	II	I	I	Partial	PCZ		III	II	Partial	
		IV	IV	None	IV	IV	None	III	III	Partial	I	I	Complete	IV	PCZ		IV	IV	None	
		IV	IV	None	IV	IV	None	IV	IV	None	III	IV	IV	Partial	TEP		IV	IV	None	

* PCZ = Prochlorperazine - Compazine; MCP = Metoclopramide - Reglan; TEP = Thiethylperazine - Torecan
 ** 2nd THC Course
 *** 2nd Placebo Course

An objection that could potentially be raised to this study is that these were patients who had in general responded poorly to antiemetics previously and, therefore, would not be expected to respond to placebo, thereby biasing the results in favor of THC. Since THC is intended to be used only when other antiemetics have failed, this is a perfectly appropriate population in which to do this study.

I consider this a pivotal study. There were no major design or methodological flaws that invalidate the results. Though the rate of ADRs was high, this is to be expected. Their self-limited nature makes the use of the drug safe in an appropriate context and patient population. Though the numbers are small, the response to THC is clinically impressive, and I accept this study as evidence that THC is effective as an antiemetic in these patients.

FRYTAK STUDY

This is a double-blind randomized study to compare THC, compazine and placebo as antiemetics in patients receiving cancer chemotherapy.

Patients - 116 patients were studied. They ranged in age from 21-70 with a median age of 61. All were undergoing chemotherapy for the first time and had either unresectable gastrointestinal cancer or were participating in a GI cancer surgical adjuvant program. They were all outpatients.

The chemotherapy was essentially standardized. Each patient was on a 5-day regimen that consisted of, at least, the following schedule:

5-Fluorouracil IV for 5 days - 300-350 mg/M²/day
Semustine - on day 1, 110-175 mg/M².

Some patients also received vincristine, doxorubicin, razoxane, or triazine. Therefore, the strongest emetic stimulus was on day 1.

Drug Schedules and Dosages

Doses were THC - 15 mgs, compazine - 10 mg given in the following way:

Day 1 - 2 hours prior to chemotherapy, then at 2 and 8 hours post-chemotherapy.

Days 2-4 - TID, 1/2 hour before meals.

Observations - Patients were seen daily by a physician. They initially volunteered information on all variables, then were specifically asked questions about them.

Efficacy Variables

Three efficacy variables were determined:

1. Occurrence of Nausea and Vomiting
 - a. no nausea or vomiting
 - b. nausea mentioned only on questioning
 - c. vomiting once
 - d. vomiting more than once.
2. Global Evaluation
 - a. complete responder - no nausea or vomiting
 - b. partial responder - nausea only
 - c. poor responder - vomiting.

(This variable was determined at day 1 only)

3. Final Outcome

After day 1 patients who vomited more than 2 times were judged failures and withdrawn. Patients who were discontinued secondary to side effects were also considered failures. Therefore, the final outcome was determined by whether or not a patient completed the study.

Safety Variables

Three specific variables were asked for:

1. occurrence of sedation
2. occurrence of coordination abnormality
3. occurrence of a "high".

Each was graded as follows:

0	none
1	on questioning only
2	volunteered.

These variables were determined daily.

Results - Adverse Effects

Patients were randomized to treatment groups in the following way:

THC	38
Compazine	41
Placebo	37

Fourteen (14) patients withdrew due to intolerable side effects - 1 on placebo (fainting), 1 on compazine (restless), 12 on THC (7 ataxia, 3 hypotension, 2 each of hallucinations, blurred vision, muddled thinking, and paresthesiae). Four patients had dysphoric reactions, all of whom were on THC and all of whom discontinued the study.

Twenty eight of 38 (74%) experienced sedation on THC; 23/38 (61%) experienced a "high"; 28/38 (74%) experienced coordination abnormalities and 10/38 (26%) were dizzy and 9/38 (24%) were shaky or unsteady. Thirty-four of 38 (89%) had side reactions of some sort on THC.

Twenty-eight of 41 (68%) of patients on compazine experience sedation, while 6/41 (15%) experienced a "high", 6/41 also experienced a coordination abnormality; 29/41 (71%) experienced a side effect of some sort.

Sixteen of 37 (16/37) or 43% experienced sedation on placebo. Seven of 37 (19%) had a coordination abnormality, and 19/37 (51%) had one or more ADR.

Efficacy -

Thirteen (13) patients withdrew from the study due to persistent vomiting - 5 on placebo, 7 on compazine, and 1 on THC.

The results obtained on day 1 are the results of interest, as this was the day of strongest emetogenic stimulus. (More on this point later).

The sponsor claims that 16/38 (42.1%) of patients on THC were complete responders, while 7/37 (18.9%) of patients on placebo were in that category. This is significant at the .05 level. No significant difference between the results of THC and compazine were found.

Analysis of day 3 shows that THC was significantly better than placebo, though not better than compazine.

Comments - Adverse Reactions

As expected, a high incidence of ADRs on THC was recorded in this study. It was responsible for essentially all the dropouts in the THC group (34% dropped out). The dropout rate was, according to statistical consultation, significantly higher ($p = .08$) for the THC group than the placebo group, and ADRs accounted for almost all of this. A fairly significant percentage of compazine patients had ADRs, though the bulk of this was sedation, a relatively mild effect. Interestingly 15% on compazine experienced a "high", as did 15% also experience a coordination abnormality - these are high rates for such ADRs and are difficult to interpret, as is an even higher 19% rate of coordination abnormality in the placebo group. Nonetheless, the THC group stands out in this regard though, as expected, these reactions are all self-limited and require no specific therapy.

Efficacy

The main positive finding here is the statistically significant difference in complete responders on day 1 between THC and placebo patients. First, I would like to make the case that day 1 is the most valid day to analyze.

Results obtained after day 1 are difficult to interpret for a number of reasons. The emetic stimulus was greatest on day 1 and provided the greatest challenge to a given antiemetic. Also, it is the day on which one expects to see an effect, if any, of an antiemetic, since the "disease" (nausea and vomiting) is at its apogee.

Crucially, the dosing of antiemetics after day 1 was on a TID basis. This did not necessarily bear any temporal relationship to chemotherapy dose (or a uniform one in any event). This temporal relationship is probably extremely important in providing protection against nausea and vomiting, and a TID dosing schedule is probably inappropriate here. Day 1 was the only day when an appropriate dosing schedule was used.

Also, since patients were dropped along the way (either due to ADRs or ineffectiveness of antiemetic therapy), the groups changed character and a selection process therefore took place for either good responders and/or those resistant to ADRs (and possibly to beneficial response?).

Also, some numbers in Table 5 do not jibe. For instance, between days 3 and 4, 3 patients dropped out of the placebo group (n = 34-31). These 3 must either have had intolerable side effects or vomiting. On day 3, 1 patient vomited twice or more (3% of n = 34). At most, therefore, 1 of the 3 who dropped out did so for vomiting, leaving 2 who must have dropped out due to intolerable side effects. Yet we know that in the entire study, only 1 placebo patient discontinued due to intolerable side effects. Therefore, there is an internal contradiction.

These reasons make it reasonable, in my view, to restrict the analysis to patients' responses on day 1.

The complete responder category is the most objective and reliable category of success of the rating scales provided, because it is clear how to interpret it. Even mean scores of the occurrence of nausea and vomiting ratings are more difficult to interpret. As mentioned earlier, these scales are most meaningful at the extremes, and the complete responder rating is just that - the extreme beneficial portion of that scale.

For these reasons, I believe that a significant difference in the number of complete responders on day 1 is a meaningful measure of drug efficacy.

TABLE 4
FINAL OUTCOME

Treatment	Total Patients	Patients Who Completed Study	Patients Who Did Not Complete Study
Placebo	37	31	6
Prochlorperazine	41	33	8
THC	38	25	13

COMPARISON OF THC AND PLACEBO

Treatment	Percent Completed	Chi-Square	P-Value
Placebo	83.8%	2.33	0.13
THC	65.8%		

COMPARISON OF THC AND PROCHLORPERAZINE

Treatment	Percent Completed	Chi-Square	P-Value
Prochlorperazine	80.5%	1.49	0.22
THC	65.8%		

APPENDICES

TABLE 4A

PATIENTS WITHDRAWN FROM STUDY DUE
TO PERSISTENT VOMITING

Treatment	Total Patients	Experienced Persistent Vomiting	Did Not Experience Persistent Vomiting
Placebo	37	5	32
Prochlorperazine	41	7	34
THC	38	1	37

COMPARISON OF THC AND PLACEBO

Treatment	Percent Experienced	Chi-Square	P-Value
Placebo	13.5%	1.72	0.19
THC	2.6%		

COMPARISON OF THC AND PROCHLORPERAZINE

Treatment	Percent Experienced	Chi-Square	P-Value
Prochlorperazine	17.1%	3.07	0.08
THC	2.6%		

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TABLE 4BPATIENTS WITHDRAWN FROM STUDY DUE
TO INTOLERABLE SIDE EFFECTS

Treatment	Total Patients	Experienced Intolerable Side Effects	Did Not Experience Intolerable Side Effects
Placebo	37	1	36
Prochlorperazine	41	1	40
THC	38	12	26

COMPARISON OF THC AND PLACEBO

Treatment	Percent Experienced	Chi-Square	P-Value
Placebo	2.7%	8.19	0.004
THC	31.6%		

COMPARISON OF THC AND PROCHLORPERAZINE

Treatment	Percent Experienced	Chi-Square	P-Value
Prochlorperazine	2.4%	10.15	0.001
THC	31.6%		

5
**SUMMARY OF RESPONSE & SIDE ACTIONS
 ACCORDING TO ANTIEMETIC STUDY DRUG**

	Day 1*		Day 2**		Day 3**		Day 4**	
	Placebo n=37	Prochlor- perazine THC n=41	Placebo n=34	Prochlor- perazine THC n=28	Placebo n=34	Prochlor- perazine THC n=26	Placebo n=31	Prochlor- perazine THC n=25
<u>Nausea & Vomiting Occurrence</u>								
None	19%	41%	68%	80%	56%	82%	77%	91%
Nausea on questioning only	5%	2%	9%	11%	12%	3%	0%	3%
Nausea volunteered	11%	0%	15%	3%	18%	6%	10%	3%
Vomiting once	14%	15%	9%	0%	12%	9%	10%	3%
Vomiting 2 or more times	51%	41%	0%	6%	3%	0%	3%	0%
<u>Sedation Occurrence</u>								
None	76%	49%	76%	64%	79%	48%	77%	52%
On questioning only	19%	36%	21%	30%	12%	45%	23%	33%
Volunteered	5%	15%	3%	6%	9%	6%	0%	15%
<u>Coordination Abnormality Occurrence</u>								
None	92%	93%	85%	94%	88%	97%	94%	91%
On questioning only	8%	5%	15%	3%	9%	3%	3%	6%
Volunteered	0%	2%	0%	3%	3%	0%	3%	3%
<u>"High" Occurrence</u>								
None	100%	98%	100%	94%	100%	94%	100%	94%
On questioning only	0%	2%	0%	0%	0%	3%	0%	6%
Volunteered	0%	0%	0%	6%	0%	3%	0%	0%
<u>Appetite Changes</u>								
Increased	0%	10%	21%	17%	18%	12%	29%	12%
Stayed the Same	46%	54%	44%	64%	41%	64%	48%	70%
Decreased	54%	36%	35%	19%	41%	24%	29%	18%

* Patients exposed to a strong emetic stimulus (5-FU and MECNU as a 2-drug combination or in a 3-drug combination with VCR, DXO, ICRF 159 or T2T).

** Patients exposed to a weak stimulus (5-FU alone).

TABLE 8

GLOBAL EVALUATION AT DAY 1
FOR NAUSEA AND VOMITING

Treatment	Total Patients	Response		
		Complete	Partial	Poor
Placebo	37	7	6	24
Prochlorperazine	41	17	1	23
THC	38	16	2	20

COMPARISON OF THC AND PLACEBO

Treatment	Complete Responders	Chi-Square	P-Value
Placebo	18.9%	3.71	0.05
THC	42.1%		

COMPARISON OF THC AND PROCHLORPERAZINE

Treatment	Complete Responders	Chi-Square	P-Value
Prochlorperazine	41.5%	0.03	0.86
THC	42.1%		

Statistical consultation has calculated the p value on the original data for this variable, which has a U distribution, and has derived a p value of .24, making this difference appear non-significant. This discrepancy arises because the sponsor's analysis grouped patients into complete responders and not complete responders, thereby contracting the data. From a clinical point of view, this contraction makes some sense. The fact that an equal number of patients in the THC and placebo groups had a poor response is important to note, but does not negate the fact that twice as many patients on THC had no nausea or vomiting. This strongly implies that there is a significant population of patients who will respond to THC who would not respond to placebo.

Statistical consultation also points out that the differences between dropouts due to persistent vomiting in the THC-placebo and THC-compazine comparisons are statistically significant, another indicator of efficacy.

In my view, this study provides supporting evidence of the effectiveness of THC as an antiemetic in patients receiving cancer chemotherapy.

UNGERLEIDER STUDY

This was a double-blind crossover study comparing THC with compazine. Patients fell into two groups:

1. Single Course - patients who received chemotherapy only on day 1 of their treatment periods.
2. Multiple Course - patients who received chemotherapy on days 2, 3, 4 and/or 5 in each period. Only the first day of this treatment was analyzed.

A washout period of 1 month was included between treatment periods.

Drug Schedules and Dosages - On each day of chemotherapy, the study drug was given 1 hour prior to chemotherapy and then every 4 hours for a total of 4 doses.

The doses of each study medication were the same and calculated according to body surface area as follows:

- <1.4 m² - 7.5 mg THC/compazine
- 1.4 m² - 1.8 m² - 10 mg THC/compazine
- >1.8 m² - 12.5 mg THC/compazine

Patients

Ages ranged from 18-82 years, with a mean age of between 46-48. There were 15 types of cancer and 69 different single or multiple drug chemotherapy regimens. Two hundred thirteen (213) patients were divided among 3 study groups:

1. Single Course - 97 patients who completed one day of chemotherapy/antiemetic treatment course on both compazine and THC.
2. Multiple Course - 40 patients who completed more than 1 day of chemotherapy in each treatment period.
3. One day non-crossover - 76 patients who dropped out of 1 or 2 above after completing one treatment but not crossing over to the 2nd treatment period. This included 37 compazine-treated patients and 31 THC-treated patients.

Patients either were continuing a previously given chemotherapy regimen, starting a different regimen, starting chemotherapy for the first time, or starting chemotherapy after having received BCG and tumor cell vaccine (immunotherapy).

Efficacy variables:

1. Occurrence of Nausea and Vomiting and Mean Hourly Difference from Pre-One Hour Score.

Seven levels of response were noted:

- 0 - no nausea
- 1 - mild nausea
- 2 - moderate nausea
- 3 - severe nausea without vomiting or retching
- 4 - no episodes of vomiting, but retching
- 5 - one episode of vomiting
- 6 - multiple episodes of vomiting

Patients were evaluated at 1 hour prior to chemotherapy and at 4, 8, 12, 16, 24 hours following the first dose of antiemetic. For the first day of each treatment period, the Mean Hourly Difference from Pre-One Hour Score was derived as follows:

For each observation point described above, the numerical value for nausea and vomiting (0-6) at the pre-one hour time was subtracted from each subsequent value. This difference was divided by the number of hours elapsed since the previous evaluation, to give an hourly difference. The mean values of these differences was computed.

2. Global Evaluation

- a. Complete responder - no nausea and vomiting
- b. Partial responder - mild or moderate nausea
- c. Poor responder - severe nausea, retching or vomiting.

3. Patient's Comparative Evaluation - Patients were asked to compare the two drugs in the following way:

- a. which drug was preferable with regard to (1) nausea, (2) vomiting and (3) overall
- b. compare the first drug to the second drug with respect to (1) overall preference and (2) control of nausea and vomiting.

Patient self-ratings were mainly performed. Outpatients were called twice/day to insure completion of questionnaire.

This was a double-dummy design.

Results - Adverse Reactions

Of 170 total patients who took THC, 15/170 (9%) experienced a "high." Twenty-seven of 170 (27/170, 16%) felt relaxed, and 59/170 (34%) experienced sleepiness. Forty-five of 170 (26%) felt dizzy and 30/170 (18%) had mental clouding. Nineteen of 170 (11%) had spatial-time disorientation and 26/170 (15%) had a dysphoric reaction. Other less frequent side effects were hunger (17%), headache (9%), short-term memory loss (8%), pleasant sensation (10%), improved sleep (7%), decreased pain (6%), and an unpleasant sensation (9%). Forty-one (24%) had no side effects.

Efficacy

Efficacy was tabulated for each of the 3 patient groups by treatment, sequence, period, sequence by treatment, and period by treatment. These were tabulated for individual scores as well as means. There was no significant difference between the antiemetic effects of THC and compazine; sequence and period effects were not significant.

The sponsor notes that those patients classified as poor responders (in the single course group) after taking compazine first, had a statistically significantly better response when switched to THC, while those who responded poorly to THC first did not significantly improve when switched to compazine.

In addition, no significant responses were detected between patient preferences, either when asked which drug they preferred or to compare drug 1 with drug 2.

Similar results are obtained for the patients in the Multiple Course Group, except no significant improvement was noted for poor responders who took compazine first when switched to THC.

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One critical limitation imposed by the study design is the use of an active control. There is no sure way to know that patients' responses were drug-related. Though means for efficacy variables were quite low (1.77/6 at maximum for THC and 1.60/6 maximum for compazine for single course patients - Table 15), and these numbers clinically translate into an extremely well-controlled patient population, we could be seeing a strong placebo response, or a weak emetogenic stimulus, or both. The different histories of the patients ~~of the patients~~ may also confound the results.

With respect to the expected placebo response, while it is true that this can not be known with any certainty, it should be stated that it is quite unlikely that placebo response would be so strong over so many patients and over so many different chemotherapy regimens. In addition, there is at least a general belief that compazine is effective to some degree in these patients (i.e., better than placebo), and therefore there is reason to believe that if THC is indistinguishable from compazine it, too, is active here.

A more trenchant objection to this active control study is that the emetogenic stimuli were very small, given the array of chemotherapies employed. However, a review of the anti-cancer regimens used reveals that many of the drugs are known to be emetogenic, and would be expected to cause significant nausea and vomiting. Therefore, I do not believe that the results can be explained on this basis.

Another major objection to studies of this kind is that since so many different chemotherapy drugs were used (and hence emetogenic stimulus not controlled for), the results are difficult to apply to specific populations. That is, what kind of statement can be made about the response of a patient taking THC to prevent the emesis associated with chemotherapy X, if not enough patients took chemotherapy X to draw any statistically valid conclusions? Therefore, how can we make a judgment as to how "potent" an antiemetic THC is? This is certainly a problem - the number of patients taking a specific chemotherapy regimen is too small to generalize about the effect of THC on the nausea and vomiting induced by those particular regimens. However, if there is an across-the-board response noted (as I believe this study documents), the drug is active in patients taking cancer chemotherapy.

This study cannot be considered pivotal. The methodological and design flaws make it impossible to conclude definitively that THC is effective as an antiemetic. However, I do feel that the study is supportive of the claim that, in this setting, THC is as effective as compazine in controlling nausea and vomiting, and that that effectiveness is not due to placebo effect.

TABLE 13

PATIENTS RESPONSE TO ANTIEMETICS ACCORDING
TO CROSS-OVER SEQUENCE AND TREATMENT

EMESIS SCALE	1ST EVALUATION TIME PRE 1 HOUR				2ND EVALUATION TIME 4TH HOUR				3RD EVALUATION TIME 8TH HOUR				4th EVALUATION TIME 12TH HOUR			
	Compazine 1st		THC 1st		Compazine 1st		THC 1st		Compazine 1st		THC 1st		Compazine 1st		THC 1st	
	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC
Nausea & Vomiting	44	45	36	36	29	30	26	26	21	27	23	25	27	27	26	26
Mild Nausea Only	10	8	3	3	9	7	5	5	12	4	8	7	5	9	4	4
Moderate Nausea	2	0	1	1	4	1	1	1	4	7	2	3	2	5	2	2
Severe Nausea	0	1	1	1	0	0	0	0	3	0	0	0	1	0	1	0
retching	0	0	0	0	2	1	1	1	1	0	1	2	1	1	1	1
Multiple Vomit	0	0	0	0	2	3	3	3	3	4	3	1	4	4	0	3
Missing Data	0	0	0	0	10	11	5	5	12	8	3	3	7	9	6	4
Totals	56	56	41	41	56	56	41	41	56	56	41	41	56	56	41	41
EMESIS SCALE	5TH EVALUATION TIME 16TH HOUR				6TH EVALUATION TIME 24TH HOUR				ENTIRE 24 HOURS *							
	Compazine 1st		THC 1st		Compazine 1st		THC 1st		Compazine 1st		THC 1st		Compazine 1st		THC 1st	
	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC
Nausea & Vomiting	35	32	29	27	30	29	28	29	9	17	14	11	9	10	14	11
Mild Nausea Only	7	3	2	6	10	6	7	5	10	6	9	9	6	10	9	9
Moderate Nausea	2	3	2	0	2	2	0	1	2	2	0	5	2	2	0	5
Severe Nausea	2	2	2	0	1	2	0	0	2	2	4	0	2	2	4	0
retching	1	1	0	2	1	0	1	1	2	0	1	3	2	2	1	3
Vomit	3	2	1	2	3	0	1	0	9	5	2	4	5	9	2	4
Multiple Vomit	3	5	2	2	3	8	0	1	22	22	11	9	22	11	9	9
Missing Data	3	8	3	2	6	9	4	4	0	2	0	0	2	0	1	0
Totals	56	56	41	41	56	56	41	41	56	56	41	41	56	56	41	41

* Values shown represent highest severity of nausea and vomiting occurrence during entire 24 hours of evaluation.

TABLE 14

Single Course
Cross-Over Trial

PATIENTS RESPONSE TO ANTIEMETICS ACCORDING
TO CROSS-OVER PERIOD AND TREATMENT

EMESIS SCALE	1ST EVALUATION TIME PRE 1 HOUR				2ND EVALUATION TIME 4TH HOUR				3RD EVALUATION TIME 8TH HOUR				4TH EVALUATION TIME 12TH HOUR			
	1st Period		2nd Period		1st Period		2nd Period		1st Period		2nd Period		1st Period		2nd Period	
	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC
No Nausea & Vomiting	44	36	36	45	29	26	30	21	25	23	27	26	27	26	27	27
Mild Nausea Only	10	3	4	8	9	6	7	12	7	8	4	5	9	4	4	5
Moderate Nausea	2	1	0	0	4	2	1	4	3	2	7	2	5	2	2	2
Severe Nausea	0	1	0	1	0	1	0	3	0	0	0	0	0	0	1	1
Retching	0	0	0	0	2	0	1	1	2	1	0	1	1	1	0	1
One Vomit	0	0	0	0	2	0	3	3	1	3	4	3	4	3	4	5
Multiple Vomit	0	0	1	2	10	6	11	12	3	3	8	9	9	6	7	7
Missing Data	0	0	0	0	0	0	3	0	0	1	6	0	1	0	1	8
Totals	56	41	41	56	56	41	56	56	41	41	56	56	41	41	56	56
EMESIS SCALE	5TH EVALUATION TIME 16TH HOUR				6TH EVALUATION TIME 24TH HOUR				ENTIRE 24 HOURS *							
	1st Period		2nd Period		1st Period		2nd Period		1st Period		2nd Period		1st Period		2nd Period	
	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC	Comp	THC
No Nausea & Vomiting	35	27	29	32	30	29	29	9	11	14	17	9	10	14	17	17
Mild Nausea Only	7	6	2	3	10	5	6	10	9	9	6	2	2	9	6	6
Moderate Nausea	2	0	0	3	2	0	2	2	5	0	2	0	0	0	2	2
Severe Nausea	2	0	0	2	1	0	2	2	0	4	2	2	2	4	2	2
Retching	1	2	0	1	1	1	0	2	3	1	0	2	2	1	0	0
One Vomit	3	2	1	2	3	0	0	9	4	2	5	2	9	2	5	5
Multiple Vomit	3	2	2	5	3	1	8	22	9	11	22	22	9	11	22	22
Missing Data	3	2	3	8	6	4	9	0	0	0	2	0	0	0	2	2
Totals	56	41	41	56	56	41	56	56	41	41	56	56	41	41	56	56

* Values shown represent highest severity of nausea and vomiting occurrence during entire 24 hours of evaluation.

TABLE 15

Single Course

MEAN RESPONSE TO ANTIEMETICS ACCORDING TO
EMESIS SCORE PER EACH EVALUATION TIME
BY TREATMENT

Evaluation Time	TREATMENT					
	Compazine			THC		
	Missing	N	Mean	Missing	N	Mean
Pre 1st Hour	1	96	0.19	2	95	0.24
4th Hour	0	97	1.48	3	94	1.60
8th Hour	1	96	1.77	6	91	1.43
12th Hour	2	95	1.56	8	89	1.52
16th Hour	5	92	0.97	10	87	1.09
24th Hour	10	87	0.80	13	84	0.96

Emesis Scores are based on scale below:

Emesis Scale:

- 0 = No Nausea & vomiting
- 1 = Mild Nausea
- 2 = Moderate Nausea
- 3 = Severe Nausea
- 4 = Retching
- 5 = One Vomit
- 6 = Multiple Vomits

Single Course
Cross-Over Trial

TABLE 22.

PATIENT RESPONSE TO FIRST DRUG COMPARED TO SAME PATIENT RESPONSE WHEN CROSSED
OVER TO SECOND DRUG DURING ENTIRE 24 HOUR EVALUATION SPAN

PATIENT RESPONSE TO COMPAZINE - 1ST DRUG	PATIENT RESPONSE WHEN CROSSED OVER TO THC							Multiple Vomit	Total
	No Nausea & Vomiting	Mild Nausea Only	Moderate Nausea	Severe Nausea	Retching	One Vomit	Multiple Vomit		
No Nausea & Vomiting	6	0	0	1	0	0	1	8	
Mild Nausea Only	5	1	0	0	0	1	3	10	
Moderate Nausea	1	0	1	0	0	0	0	2	
Severe Nausea	0	2	0	0	0	0	0	2	
Retching	0	0	0	0	0	1	1	2	
One Vomit	4	1	1	1	0	0	2	9	
Multiple Vomit	1	2	0	0	0	3	15	21	
Totals**	17	6	2	2	0	5	22	54	
PATIENT RESPONSE TO THC - 1ST DRUG	PATIENT RESPONSE WHEN CROSSED OVER TO COMPAZINE							Multiple Vomit	Total
	No Nausea & Vomiting	Mild Nausea Only	Moderate Nausea	Severe Nausea	Retching	One Vomit	Multiple Vomit		
No Nausea & Vomiting	7	1	0	2	0	0	1	11	
Mild Nausea Only	3	4	0	1	0	0	1	9	
Moderate Nausea	1	2	0	1	0	0	1	5	
Severe Nausea	0	0	0	0	0	0	0	0	
Retching	1	0	0	0	0	0	2	3	
One Vomit	2	0	0	0	0	1	1	4	
Multiple Vomit	0	2	0	0	1	1	5	9	
Totals	14	9	0	4	1	2	11	41	

* Values shown represent highest severity of nausea & vomiting occurrence during entire 24 hours of evaluation.

TABLE 23

Single Course
Cross-Over Trial

PATIENT RESPONSE TO FIRST DRUG COMPARED TO SAME PATIENT RESPONSE WHEN
CROSSED OVER TO SECOND DRUG DURING ENTIRE 24 HOUR EVALUATION SPAN

RESPONSE TO COMPAZINE - 1ST DRUG **	RESPONSE WHEN CROSSED OVER TO THC		
	Responded Same No. (%)	Responded Better No. (%)	Responded Worse No. (%)
8 (15) Complete Responders	6 (75)	0 -	2 (25)
12 (22) Partial Responders	2 (17)	6 (50)	4 (12)
<u>34</u> (63) Poor Responders	<u>15</u> (44)	<u>15</u> (44)	<u>4</u> (12)
54 (100)	23 (43)	21 (39)	10 (18)
RESPONSE TO THC - 1ST DRUG	RESPONSE WHEN CROSSED OVER TO COMPAZINE		
11 (27) Complete Responders	7 (64)	0 -	4 (36)
14 (34) Partial Responders	6 (43)	4 (28)	4 (29)
<u>16</u> (39) Poor Responders	<u>6</u> (37)	<u>7</u> (44)	<u>3</u> (19)
41 (100)	19 (46)	11 (27)	11 (27)
Complete Response = No Nausea & Vomiting Partial Response = Mild or Moderate Nausea Poor Response = Severe Nausea; Retching; One Vomit; or Multiple Vomit Episodes			

* Values shown represent highest severity of nausea and vomiting occurrence during entire 24 hours of evaluation

** Data missing for comparison in 2 cases.

SCHEIN STUDY

This is a double-blind crossover study comparing THC with compazine. It was originally designed as a four-period crossover study, but since only 13/32 patients finished all four treatment periods, it was analyzed as a two-period crossover study.

Patients - Thirty-two (32) patients with 12 types of cancer and 26 different single or combination chemotherapy regimens were included. There were 23 females, 9 males, and 29 outpatients and 3 inpatients.

Drug Schedules and Dosages

Patients took the study antiemetic 1 hour prior to chemotherapy and every 4 hours thereafter for no more than 48 hours after the start of the chemotherapy. The doses of antiemetics were:

THC - 15 mg/M² -
Compazine - 10 mg

Efficacy Variables1. Severity of Nausea

- 0 - none
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - incapacitating

2. Duration of Nausea

The total duration of nausea during each treatment.

3. Severity of Vomiting

- 0 - none
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - incapacitating

4. Number of Vomiting Episodes

Calculated by multiplying the frequency/hour by the duration of observations.

5. Patient's Evaluation

Patients were asked to select which treatment was best (if any).

6. Investigator's Global Evaluation - classified as follows:

- a. Complete responder - no vomiting and no, or slight, nausea
- b. Partial responder - moderate vomiting and/or nausea
- c. Poor responder - severe vomiting and/or nausea.

7. Final Outcome - Patients were classified as to whether they completed at least one course of each study drug.

The data utilized in the efficacy analysis were the results of the first period in which each study drug was used. Only those patients who completed at least one course each of THC and compazine were included in the analysis of variables 1-6 above. All patients were included in the analysis of variable 7.

Observations - Patients recorded in a diary the ratings described above. There was one score for variables 1 and 3 for each observation period.

Results - Adverse Reactions

All 32 patients who took THC had a side effect of some sort. Eight (8) (25%) had a "high". Eight (25%) also experienced dizziness, and 8 were drowsy. Nine patients (28%) were weak, had an unsteady gait, or were otherwise unable to move. Four patients (12%) were confused and disoriented. Six (19%) had visual distortions or double vision; 3 patients had hallucinations, and 4 (12%) were paranoid. Fifteen patients (47%) had dysphoric reactions, and 14 (44%) had other unpleasant reactions. Three patients (9%) had a pleasant experience only. Twelve patients (12) discontinued the study due to THC side effects.

Only 2/21 (9%) patients had adverse reactions on compazine. Each felt drowsy, and 1 in addition had a "drugged" feeling.

Efficacy

Eighteen (18) patients received THC first; 14 received compazine first. Only 7/18 (38.9%) who took THC first crossed over to compazine. All patients who took compazine first crossed over to THC. This difference was significant at the .001 level. Six of the 11 who did not cross over did so due to severe side effects of THC. Two discontinued because they got no relief from THC; the remaining 3 discontinued for reasons that are unclear.

The sponsor makes the following claims for the superiority of THC over compazine.

Table 9 purports to show THC superior to compazine because 11/21 did better on THC than compazine in the nausea variable and 13/21 did better on THC than compazine for the vomiting variable. Results of the sign test show these differences to be clinically significant at $p = .006$ and $.001$ respectively.

Table 10 purports to show that THC positively effected the duration of nausea and number of vomiting episodes as compared to compazine.

The sponsor notes that of the 21 patients who received both antiemetics, 16 indicated a preference, and 15/16 preferred THC, while 1/16 preferred compazine. This was a significant difference at the $.001$ level.

The sponsor also claims that patients who did poorly on compazine as a first drug improved considerably upon crossing over to THC. (Table 12).

Comments - Adverse Reactions

The incidence of side effects was obviously high, as all patients who took THC had reactions to it. The usual ADRs were noted, but a relatively high rate of dysphoric reactions (47%) was seen. This is possibly because the dose of THC used in this study was large - 15 mg/M^2 . The high rate of this severe reaction provides useful safety information about acceptable dose ranges of THC, and will be discussed later.

Efficacy

The claim that THC is better than compazine in controlling severity of nausea based on 11/21 improved is subject to some question. If these 11 patients are examined, one finds that in only 6 was their rating improved by more than 1 point. This means that 5/11 improved only 1 point on the rating scale - a difference this is not terribly meaningful from a clinical point of view, as the truly important changes occur between end-points on the rating scales. With regard to severity of vomiting, 10/13 who improved on THC did improve by 2 or more points, a more impressive figure.

As regards the duration of nausea, this was significantly related to period, and so is not unambiguously a drug-related effect.

A particularly strong bias exists in the analysis of this study. Eleven (11) patients received THC, but never received compazine. These 11 are never analyzed with regard to efficacy. They have been removed from the efficacy analysis, even though some of them discontinued the study specifically because THC was ineffective. To analyze only those THC patients (21) who did well enough to complete the study seriously biases the analysis. For example, the

means of these 11 patients on the four outcome variables is calculated below, and compared with the means calculated by the sponsor.

	<u>Nausea Sev.</u>	<u>Nausea Dur.</u>	<u>Vomit Sev.</u>	<u>#Vomiting Episodes</u>
11 patients	2.54	16.0	2.27	6.27
21 patients	1.86	13.31	1.62	4.62

While the figures are not very different for these 11, as compared to the 21 the sponsor analyzed, they do suggest that excluding these patients biases conclusions in favor of THC.

In addition, 6/11 were classified poor responders, 3 were partial, and 2 complete. This compares with 4/21 poor responders, 9/21 partial responders, and 7/21 complete responders for the patients the sponsor did analyze.

Given this bias, it is difficult to accept the judgments made by the sponsor in favor of THC. We cannot say, for example, how many of these patients would have improved when switched to compazine; therefore, the fact that 11/21 or 13/21 did better on THC on the severity variables is not necessarily an impressive testimony in favor of THC - it is incomplete testimony.

With reference to the patient preferences, I feel this is a meaningful variable, but again the exclusion of the 11 who did not cross over makes the case look more favorable than it might really be. Seven (7) of these 11 had no preference, when compared to a previous trial of compazine. Of the total 32, 13 did not choose THC. This does not change the number of those who did prefer THC (in fact, an additional 3 of these 11 patients chose THC), but it does indicate that 13/32 did not choose THC, as opposed to 6/21, as the sponsor claims.

I would also add that the claim of improvement of poor compazine responders who were switched to THC suffers when these excluded 11 are looked at. As mentioned earlier, 6/11 were poor responders on THC - we simply have no way of knowing how these patients would have done if switched to compazine. This uncertainty severely calls into question the sponsor's conclusions in these areas. (Also, 2 patients were classified incorrectly as poor responders on compazine ~~_____~~)

I believe in general, the sponsor's claims of superiority of THC over compazine are not definitively supported by the data, for the reasons stated above. However, even if one gives to all 11 excluded patients ratings in favor of compazine, the results still would not show a superiority of compazine - at the worst (for THC), the drugs would be shown to be essentially comparable in most parameters. For instance, if all 11 would have responded better to compazine (impossible, since 2 were complete responders), then Table 9 would read as follows:

	<u>Compazine Better</u>	<u>Same</u>	<u>THC Better</u>
Severity of Nausea	12	9	11
Severity of Vomiting	11	8	13

There is no difference, in this case, between THC and compazine.

If one looks at global assessment (Table 12), the top box becomes:

<u>Tx sequence</u>	<u>Response</u>		
	<u>Poor</u>	<u>Partial</u>	<u>Complete</u>
Compazine - 1st	13	1	0
THC - 1st	8	4	6

Here we see that 14 in the compazine 1st group had the potential to improve - 11 actually did. (11/14)

Now, 12 in the THC group would have had the potential to improve - if all improved (very unlikely), then 12/12 would have improved on the global rating. These ratios are comparable, though better for compazine.

If we look at patient preferences, if we negate the preferences given by the patients (on the basis of their unreliability) and attribute a preference to each for compazine, then 11/32 preferred compazine, 15/32 preferred THC, again, a small difference.

The study, therefore, in my view fails to distinguish between the efficacy of THC and compazine as antiemetics in this setting, when all patients are included in the analysis and with the most "conservative" assumptions having been made. This failure may be as a result of a lack of power to detect a difference, or the drugs may in fact be comparable in effectiveness. I suspect that this study would not have sufficient power to uncover the presumably small difference we might expect to see between these two treatments.

Other problems that hamper interpretation of the data are those mentioned earlier. Multiple chemotherapy regimens introduce a confounding factor (particularly if treatments are indistinguishable), and an active control study can never unequivocally be said to show that any effect was not due to a placebo response.

Also, one wonders about the comparability of the doses used between treatments. This study used a high dose of THC, which may have accounted not only for the ADRs seen, but its "effectiveness." While 10 mg of compazine is an accepted dose, it may not compare in strength to 15 mg/M² of THC.

TABLE 3FINAL OUTCOME

Sequence Group	Total Patients	Crossed Over	Did Not Cross Over
THC - 1st	18	7	11
Prochlorperazine - 1st	14	14	0

CHI-SQUARE TEST

Sequence Group	Percent Crossed Over	Chi-Square	P-Value
THC - 1st	38.9%	10.47	0.001
Prochlorperazine - 1st	100.0%		

TABLE 6
MEAN RESPONSE TO ANTIEMETICS FOR
EACH EFFICACY VARIABLE FOR
TREATMENT, SEQUENCE, AND PERIOD

Variable		Treatment		Sequence		Period	
		P	THC	P - 1st	THC - 1st	1	2
Nausea Severity	N MEAN	21 2.71	21 1.86	28 2.43	14 2.00	21 2.52	21 2.05
Nausea Duration (Hr.)	N MEAN	21 21.40	21 13.31	28 16.98	14 18.11	21 19.57	21 15.14
Vomiting Severity	N MEAN	21 2.95	21 1.62	28 2.43	14 2.00	21 2.48	21 2.10
Number of Vomiting Episodes	N MEAN	21 11.67	21 4.62	28 8.89	14 6.64	21 11.14	21 5.14

Severity scores are based on scale below:

Severity Scale

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

TABLE 9RESULTS OF SIGN TEST FOR SEVERITY
OF NAUSEA AND VOMITING

Variable	Prochlor- perazine Better	Same	THC Better	Binomial P-Value
Severity of Nausea	1	9	11	0.006
Severity of Vomiting	0	8	13	0.001

TABLE 11PATIENT EVALUATION OF TREATMENT

	Prochlor- perazine Better	Same	THC Better	Total
Number of Patients	1 4.8%	5 23.8%	15 71.4%	21

Patients Who Preferred One Drug

Treatment Preferred	Patients		Binomial P-Value
	N	%	
Prochlorperazine	1	6.25%	0.001
THC	15	93.75%	
Total	16		

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TABLE 12

INVESTIGATOR'S GLOBAL
ASSESSMENT OF RESPONSE

Treatment Sequence	Response		
	Poor	Partial	Complete
Prochlorperazine - 1st	13	1	0
THC - 1st	2	1	4

Results of Poor Responders Upon Cross-Over

Prochlorperazine - 1st, THC - 2nd	3	8	2
THC - 1st, Prochlorperazine - 2nd	1	1	0

Results of Partial or Complete Responders Upon Cross-Over

Prochlorperazine - 1st, THC - 2nd	0	0	1
THC - 1st, Prochlorperazine - 2nd	4	1	0

McNemar Test	Proportion With Better THC Response	Significance Level ^a
Prochlorperazine - 1st, THC - 2nd	$\frac{11}{11} = 100\%$	0.002
THC - 1st, Prochlorperazine-2nd	$\frac{5}{6} = 83.3\%$	0.376

^a Binomial Distribution used as numbers were small.

CHRONOLOGY OF PATIENT EXHIBIT SCORES ACCORDING TO DRUG SEQUENCE

Patient Study #	Age	Sex	Drug Sequence Courses				Nausea Severity (Scale 0-4) Courses				Nausea Duration (Hours) Courses				Vomiting Severity (Scale 0-4) Courses				Vomiting Episodes Courses				Investigator's 2 Assessment of Response TNC	Patient's Drug Preference (TNC vs Comp)
			1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th		
[REDACTED]	[REDACTED]	[REDACTED]	TNC	TNC	TNC	TNC	3	3	3	3	12	continuous (24)			3	3	3	3	9	0	0	0	Poor	eSame
			TNC	TNC	TNC	TNC	3	3	3	3	6	6	6	6	3	3	3	3	0	0	0	0	Poor	eSame
			TNC	TNC	TNC	TNC	4	4	4	4	9	9	9	9	4	4	4	4	10	10	10	10	Partial	eSame
			TNC	TNC	TNC	TNC	2	2	2	2	36	36	36	36	2	2	2	2	24	24	24	24	Partial	eSame
			TNC	TNC	TNC	TNC	3	3	3	3	72	72	72	72	3	3	3	3	0	0	0	0	Complete	eSame
			TNC	TNC	TNC	TNC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Complete	eNone
			TNC	TNC	TNC	TNC	1	1	1	1	4	4	4	4	2	2	2	2	12	12	12	12	Partial	eTNC
			TNC	TNC	TNC	TNC	3	3	3	3	48	48	48	48	3	3	3	3	16	16	16	16	Poor	eSame
			TNC	TNC	TNC	TNC	4	4	4	4	24	24	24	24	4	4	4	4	10	10	10	10	Poor	eSame
			TNC	TNC	TNC	TNC	2	2	2	2	24	24	24	24	1	1	1	1	2	2	2	2	Partial	eTNC
			TNC	TNC	TNC	TNC	1	1	1	1	3	3	3	3	0	0	0	0	0	0	0	0	Complete	eSame
			TNC	TNC	TNC	TNC	1	1	1	1	34	34	34	34	0	0	0	0	0	0	0	0	Complete	eTNC
			TNC	TNC	TNC	TNC	1	1	1	1	5	5	5	5	0	0	0	0	0	0	0	0	Complete	eTNC
			TNC	TNC	TNC	TNC	0	0	0	0	0	0	0	0	1	1	1	1	3	3	3	3	Complete	eTNC
			[REDACTED]	[REDACTED]	[REDACTED]	Comp TNC	Comp TNC	Comp TNC	Comp TNC	3	3	3	3	11	11	11	11	3	3	3	3	12	12	12
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	6	6	6	6	0	0	0	0	8	8	8	8	Poor	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	48	48	48	48	3	3	3	3	16	16	16	16	Poor	eSame
Comp TNC	Comp TNC	Comp TNC				Comp TNC	1	1	1	1	24	24	24	24	0	0	0	0	0	0	0	0	Complete	eSame
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	24	24	24	24	3	3	3	3	5	5	5	5	Poor	eSame
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	9	9	9	9	4	4	4	4	15	15	15	15	Complete	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	6	6	6	6	3	3	3	3	9	9	9	9	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	4	4	4	4	60	60	60	60	4	4	4	4	7	7	7	7	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	2	2	2	2	4	4	4	4	1	1	1	1	4	4	4	4	Complete	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	4	4	4	4	60	60	60	60	4	4	4	4	16	16	16	16	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	10	10	10	10	4	4	4	4	12	12	12	12	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	4	4	4	4	48	48	48	48	4	4	4	4	36	36	36	36	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	2	2	2	2	10	10	10	10	3	3	3	3	6	6	6	6	Partial	eTNC
Comp TNC	Comp TNC	Comp TNC				Comp TNC	3	3	3	3	5	5	5	5	4	4	4	4	30	30	30	30	Partial	eTNC

4 Comparison made between present trial of TNC and a previous trial of Compazine.
 ** Unable to compare - no prior Compazine trial.

4 0-4 Severity Scale: 0 = None
 1 = Mild
 2 = Moderate
 3 = Severe
 4 = Incapacitating

9 Investigator's Assessment Scale:
 Complete = No vomiting and none or slight nausea
 Partial = Moderate vomiting and/or nausea
 Poor = Severe vomiting and/or nausea

I believe that while this study does not support the contention that compazine is better than THC, neither does it support, in any but the most minor way, the claim that THC is as good or better than compazine as an antiemetic, or that it is better than placebo.

LEVITT STUDY

This was a double-blind, randomized study to compare the antiemetic effects of three doses of THC to compazine, placebo, and no treatment.

Patients - 117 patients were included in the analysis. Ages ranged from 20-79, with a mean age of 57.3. They had a total of 10 different types of cancer, and received 38 different single or multiple chemotherapy regimens. None had had any prior chemotherapy.

Drug Schedules and Dosages - Doses of THC were 5, 10, 15 mg; compazine was 10 mg. The initial dose of drug was given 2 hours prior to chemotherapy, followed by doses 4, 8 and 12 hours after the initial dose.

Efficacy Variables

1. Occurrence of Nausea

0 - none

1)

2)

3) 1-5 not specified

4)

5)

6 - constantly

2. Occurrence of Vomiting

The actual number of times vomiting occurred in the 24-hour evaluation period.

3. Duration of Nausea

The total time in hours that nausea occurred.

4. Time of Onset of Nausea

The time in hours that nausea began after chemotherapy as instituted.

5. Duration of Vomiting

The time span over which vomiting occurred.

6. Time of Onset of Vomiting

The time in hours that vomiting began after chemotherapy was started.

7. Investigator's Assessment of Response

ellent - no vomiting or nausea

Good - no vomiting, some nausea

Fair -

a. Tolerable vomiting, with or without tolerable nausea

b. Severe, but tolerable nausea, with or without tolerable vomiting

Poor - Intolerable vomiting or nausea persisting after the second antiemetic dose

8. Treatment failure -

Those who are poor responders

9. Final Outcome

Defined as whether or not patients started a second course of treatment.

(Patients were to complete 2 courses of chemotherapy which were administered over a 2-hour period or less, and with an interval between courses of not less than 1 week).

Safety Variables

Two (2) safety variables were analyzed statistically

1. Drowsiness

0 - none

1)

2)

3) 1-5 not specified

4)

5)

6 - constantly

2. Depression/Elation

-3 most depressed
 -2
 -1
 0 none
 +1
 +2
 +3 most elated

Observations

Patients were observed in hospital for 14 hours following the chemotherapy dose. They were monitored by either a psychiatry resident or a research nurse. Blood samples for THC levels were also taken.

Results - Adverse Reactions

Drowsiness occurred in approximately 70% of all groups

THC - 73%
 Compazine - 67%
 Placebo - 77%
 Control - 61%

Non-severe depression was noted in 23%, 29%, 41%, and 8% of the THC, compazine, placebo and control groups, respectively. Severe depression occurred in 25% of the THC group; the next highest incidence was 8% in the control group. Only 12% of the THC group were elated, the smallest of the percentages (placebo 14%, control, 28%, compazine 24%). Twenty-three (23) percent of the THC group had a time perception change, which was the only ADR which seemed to be dose-related. (12% - 5 mg, 25% - 10 mg; 37% - 15 mg). Non-severe anxiety was seen in almost 50% of all groups except the compazine group, in which it was seen in 24%.

Efficacy

127 patients entered the study. Eight (8) never received medication. Two (2) did not complete a complete course. Therefore, 117 patients were analyzed and distributed as follows:

	<u>Patients</u>
THC - 5 mg	16
THC - 10 mg	16
THC - 15 mg	16
Compazine	21
Placebo	22
Control	26

As can be seen from the tables, no statistically significant differences were found either within THC groups, or between THC-treated patients and other groups, in any of the efficacy variables evaluated.

Comments

The study on the face of it is negative. However, I would just raise a number of questions about the validity of the results.

First, one of the most important variables ((occurrence of nausea) did not have a defined scale except for none, and constantly, yet had 5 grades covering this intermediate area. This certainly raises questions about the validity of at least this variable.

Also, the very high rates of ADRs seen on all groups in this study may indicate that this population was, in some undetermined way, different from some of the others studied. A 70% incidence of drowsiness in all groups is unexpected, as is the high rate of depression seen, almost twice the rate (41% to 23%) in the placebo vs. the THC group. Likewise, an almost 50% incidence of anxiety in the placebo and THC group is perplexing.

These points make the study interesting, and may be questionable, but must be accepted, on its terms, as being negative.

EKERT STUDY

This study was done on children who had previously received a standard antiemetic while receiving chemotherapy and who had been judged to have had at least moderate nausea and vomiting.

Patients - 13 boys and 5 girls with ages ranging from 3-18 (mean age 10.3) were studied. They had a total of 7 different types of cancer and received 14 different chemotherapy regimens.

Drug Schedules and Dosages

Metaclopramide was given as the first antiemetic to 16 children and compazine in the remaining 2, in the following ways:

Metaclopramide - 10 mg - surface area $> .7M^2$
5 mg - surface area $< .7M^2$

It was given 2 hours prior to chemotherapy, then at 8, 16, and 24 hours after the first dose.

Compazine - surface area $.7M^2 - 1.1M^2$ - 5 mg 2 hours before chemotherapy, then at 8, 16, and 24 hours after chemotherapy.

surface area 1.1 - 1.4M² - 10 mg 2 hours prior to chemotherapy, 10 mg at 8 hours, and 5 mg at 16 and 24 hours after chemotherapy was begun.

surface area 1.4m² - all doses 10 mg.

In both of the above groups, a 4-hour dose was given, but was a placebo, to avoid "neurological" toxicity.

THC - 10 mg/M² with a maximum of 15 mg. It was given 2 hours prior to chemotherapy, then at 4, 8, 16, and 24 hours after the first dose.

Efficacy Variables

1. Occurrence of Nausea
 - a. None
 - b. Moderate, activity not interfered with
 - c. Severe, activity interfered with.
2. Occurrence of Vomiting
 - a. No vomiting for 24 hours
 - b. Moderate, less than 5 times in the 24 hours.
3. Overall Response
 - a. Complete responder - no nausea or vomiting
 - b. Partial response - grade 2 nausea or vomiting
 - c. No response - grade 3 nausea or vomiting.

Observations - Parents and families completed a questionnaire which assess the presence of nausea and vomiting as well as side effects, with emphasis on the detection of symptoms suggestive of a "high." When patients received chemotherapy in the hospital, the responses were gauged by the nurses.

Results - Adverse Reactions

Two (2) of 11 patients experienced a "high", and 13/18 (72%) developed somnolence. Three of 11 (17%) experienced tachycardia and 1 patient each developed ataxia and blurred vision. Four patients (22%) had no side effects at all. None had a dysphoric reaction, and none were discontinued due to side effects.

Efficacy

The statistical methods employed were the McNamara Chi-Square test. Since sequence effects confound the direct effects of THC in this trial (this is essentially a crossover with everyone receiving THC second), the analysis is only able to detect the effects of THC following another antiemetic. This was done by comparing the number of patients showing improvement. In addition, the proportion of complete responders was estimated with 95% confidence intervals calculated using the normal approximation to the binomial distribution.

The charts appended are basically self-explanatory.

Previous response	Mod. Severe	THC (nausea)			(vomiting)		
		None 3	Mod 3	Severe 1	None 4	Mod 3	Severe 1
		7	1	3	6	2	2

McNemar Test

THC-change

	Same	Better	Worse	Chi-Square	P-value
Nausea	6	11	1	6.75	.01
Vomiting	5	12	1	7.69	.01

In addition, 9/18 or 50% experienced a complete response, with a 95% confidence interval of 26.9% - 93.1%.

Comments - Adverse Reactions

While a large percentage of patients developed somnolence on THC, it was otherwise very well tolerated, with a low incidence of "highs", and no dysphoria. Children appear to be a particularly resistant group to ADRs with THC.

Efficacy

A number of design faults here prevent the unquestioning acceptance of the results as presented. Still, the data do appear to support the sponsor's claims.

A major fault in this study is that all patients took THC secondly and, therefore, perhaps important sequence effects can not be accounted for. No manipulation of the data can completely overcome this shortcoming. However, the results are rather impressive, with twice as many patients for each

variable responding better to THC than they did on their previous medication. (Seven of 9-78% of the complete responders improved by 2 grades from their previous scores). While such responses could, I suppose, be due to placebo/sequence effects, it is unlikely.

These patients were apparently selected to receive THC on the basis of a poor response to the first antiemetic. Therefore, this is a select population and does not (perhaps) fairly represent patients who did well on the first antiemetic. To my mind, the study of this "biased" sample poses no real problem, as the drug is intended for use in patients who have been refractory to other antiemetics.

Another objection to be raised is that the numbers are small, and there were so many different chemotherapy regimens that no conclusions can be drawn about THC's effects on the nausea and vomiting produced by each one. However, as mentioned in an earlier review, such a positive response, occurring across the board, indicates a generally active antiemetic property.

A separate problem is that every second dose of metaclopramide or compazine was a placebo and, therefore, the true effects of the first antiemetic might not have been accurately measured. This might make THC appear to be better than the standard when, in fact, it might not be. While this is perhaps true, the interpretation of the results could then be altered to describe THC's effect compared to placebo, which in no way detracts from the results obtained (I suppose one could say that the results seen on the first antiemetic were actually worse than placebo because a rebound effect might have occurred between the first and third doses of antiemetic; that is far-fetched at best).

While these flaws do diminish the validity of the study they do not, in my view, make the results unusable. They are supportive of the efficacy of THC as an antiemetic in this population.

(To speak to an objection raised by statistical consultation - he states that the definition of complete responder is vague, with patients with grade 2 nausea able to fit the criteria. This is no problem, as only those patients who were grade 1 in both categories were classified as such.)

LASZLO STUDY

This was an open study of THC in patients who were known to be unresponsive to a previously administered antiemetic (persistent moderate-severe) nausea and vomiting), or who were starting a treatment regimen which is known to be refractory to standard antiemetics.

Patients - 113 patients were studied. They ranged in age from 18 to 72. There were 21 types of cancers that were treated with 41 different single or combination chemotherapy regimens.

Drug Schedules and Dosage

The first 9 patients were treated with 15 mg/M² of THC every 6 hours, starting one hour before chemotherapy and continuing for 4 doses. This resulted in a very high incidence of severe side effects and, therefore, the dosage schedule was switched to 5 mg/M² every 4 hours starting 8-12 hours prior to chemotherapy was commenced for 4 doses. Some patients received chemotherapy for several days; in these patients, THC was given throughout the course.

Prior antiemetic exposure in these patients was as follows (number of trials):

- 76 - compazine
- 21 - thorazine
- 2 - torecan
- 2 - promethazine
- 1 - Tigan
- 1 - Vistaril

Twenty (20) patients starting a new regimen of high dose cyclophosphamide followed by total body irradiation, or carmustin had not received previous antiemetics, but were included because of the refractoriness to antiemetics of nausea and vomiting caused by these agents.

Observations - Prior response to antiemetics was documented by history. During the course of chemotherapy, each patient was observed by the investigators who reviewed nurses' notes, food intake, and history from the patients and their families (outpatients).

Efficacy Variables

1. Occurrence of Vomiting
 - a. no vomiting 24 hours after chemotherapy
 - b. mild vomiting 5 times
 - c. moderate vomiting - 5-10 time
 - d. severe, 10 times, patient bedridden
2. Occurrence of Nausea
 - a. none
 - b. mild, activity not interfered with

- c. moderate, activity interfered with
- d. severe, bedridden for more than 2 hours.

3. Overall Response

Complete response - no nausea and no vomiting.

Partial response - Grade 2 or 3 nausea and vomiting, and at least a 50% reduction of nausea and vomiting in patients previously refractory.

No response - Grade 4 nausea and vomiting, and 50% reduction in nausea and vomiting in previously refractory patients.

Analysis - Since there can be no direct comparison with the effects of another agent, an estimation of the true response for THC using the binomial distribution with 95% confidence intervals for proportions using the normal distribution was determined. These calculations were made for those patients who had failed previously on other antiemetics.

Results - Adverse Effects

Patients were specifically questioned about the occurrence of a "high", somnolence and appetite changes, as well as to report any other side effects noted.

Five (5) patients were discontinued secondary to side effects of THC. Three had severe dysphoric reactions (fear, anxiety, time distortions, hallucinations); one patient did not like the somnolence and one more did not like "the feeling." Two of these were in the original group of nine who received the high dose of THC. There were four other dysphoric reactions, one of which occurred in the high dose group.

There was intense somnolence in four other patients. One hundred of 113 (88%) experienced a "high" as did 88% experience somnolence. Fifty-one of 113 (44%) had dry mouth, and 17% had dizziness. Other much less frequent ADRs included blurred vision (7%), and time distortion, fear and anxiety, and hallucinations (5% each).

Efficacy

As depicted, 26 patients (24.1%) had no vomiting and 39 patients (36.1%) had mild vomiting. Twenty-four (24) patients (22.2%) had no nausea and 37 patients (34.3%) had mild nausea. Twenty-two (22) patients (20.4%) were complete responders. The 95% confidence limit were as follows:

<u>Response</u>	<u>Variable</u>	<u>95% Confidence Interval</u>
None	Vomiting	16 - 32.2%
None	Nausea	14.4 - 30%
Complete	Overall	12.8 - 28.0%

The rate of complete responders is considered statistically significant by the sponsors.

Comments

The design flaws of this study limit the usefulness of the results; however, they can be considered weakly supportive of a beneficial effect of THC on chemotherapy-induced nausea and vomiting.

The major flaw in design is that, apparently, the historical responses obtained on the first antiemetic were obtained retrospectively and by history. The accuracy of this information is, therefore, difficult to gauge, and we cannot positively know that all patients in this study were previously refractory.

In addition, it is unacceptable to consider the results obtained for the 20 previously untreated patients as valid. One cannot assume that their symptoms would have been refractory to standard antiemetics. This represents a use of the worst kind of "historical" control. The breakdown of these 20 is as follows:

14 - BCNU	6/14 - complete responders
5 - CTX	5/5 - no response
1 - TBI	1/1 - partial response

Totaled, this reveals a 30% complete response rate.

Therefore, a recalculation of the efficacy variables excluding these patients reveals:

<u>no vomiting</u>	19/88 = 21.6% (as opposed to 24.1%)
<u>no nausea</u>	17/88 = 20% (as opposed to 22.2%)
<u>complete responders</u>	16/88 = 18.2% (as opposed to 20.4%)

There does not appear to be a significant change in those percentages.

From a clinical standpoint, these numbers do have meaning. While we cannot say with complete certainty that the historical data obtained about 'patients' prior responses is accurate, we can say that about 1/5 of the patients in this trial had an excellent response, however defined. This clearly differs from their previous responses, as they were required to have had a previously quite

poor response in order to be included in the study. We can be relatively certain that, in any event, their prior responses were not excellent. Of course, it is possible that multiple changes in the intervening period between treatments could have changed the population (disease state, etc.) in ways that can never be known. Still, the dramatic response noted here is at least suggestive (and supportive) of activity of THC as an antiemetic.

Side effects were typical, with a fairly large percentage (88%) of "highs." There were only 7 dysphoric reactions, however, and in general the medication was well tolerated.

TABLE 5

DISTRIBUTION AND 95% CONFIDENCE LIMITS OF RESULTS FOR
NAUSEA, VOMITING AND OVERALL
RESPONSE VARIABLES

<u>Response</u>	<u>Vomiting</u>		<u>Nausea</u>		<u>Overall</u>		
	<u>Patients</u>		<u>Patients</u>		<u>Response</u>	<u>Patients</u>	
None	26	(24.1%)	24	(22.2%)	Complete	22	(20.4%)
Mild	39	(36.1%)	37	(34.3%)	Partial	57	(52.8%)
Moderate	14	(13.0%)	18	(16.6%)	None	29	(26.8%)
Severe	29	(26.8%)	28	(26.7%)			
Total	108		108			108	

Confidence Limits - 95%

<u>Response</u>	<u>Variable</u>	<u>Proportion (%)</u>	<u>95% Confidence Interval</u>
None	Vomiting	(24.1%)	16.0% - (32.2%)
None	Nausea	(22.2%)	14.4% - (30.0%)
Complete	Overall	(20.4%)	12.8% - (28.0%)

ADRIAMYCIN/CYTOXAN

This was a placebo controlled, randomized crossover trial to test the effects of THC on the nausea and vomiting induced by Adriamycin and Cytosin.

Patients - Six (6) males and 3 females (ages 17-58, median 41 years) who had soft tissue sarcomas were studied. They had all had surgical removal of their tumors and were clinically disease-free. They all received Adriamycin and Cytosin.

Drug Schedules and Dosages - Adriamycin and Cytosin were given every 4 weeks until a total cumulative dose of Adriamycin of 500-550 mg/M² was reached. Both Adriamycin and Cytosin were given at constant doses of, respectively, 70 and 700 mg/M² in each patient in a single 1-1/2 hour i.v. infusion.

THC - 10 mg/M² - patients were offered a THC cigarette (17.4 mg THC) if a vomiting episode occurred.

The initial dose of study drug was given 1 hour prior to chemotherapy, then at three-hour intervals for a total of five doses, and patients were rated every wakeful hour from 7:00 a.m. to midnight (these patients were hospitalized).

Efficacy Variables

As in previous

Results

Six patients were randomized to THC-placebo, three to placebo-THC. Seven of 9 (7/9) had a "high" on THC; 2 of these 7 also had a "high" on placebo. Six had drowsiness on THC; 4 on placebo. Less common ADRs on THC were hunger (2), anxiety (2) and dry throat (3). One patient had no ADRs on THC. Five placebo patients had ADRs, including depression (1), disorientation (2), hunger (1) and anxiety (1). Two patients on each treatment were disoriented, one patient being disoriented on both treatments.

Efficacy -

This study revealed no significant difference between THC and placebo, with the exception of 7/8 patients rating THC "poor" compared to placebo.

Comments

This study finds no differences between placebo and THC effects on nausea and vomiting in this population. The reasons for this might include the following:

The numbers in this study were small, and if a true, but small difference existed between the two treatments, this study would not have had the power to determine it. Of course, the truth could be that there is no difference between the two.

The real possibility exists that THC is ineffective against the nausea and vomiting caused by these two specific anti-cancer drugs, either alone or in combination. They are regarded as potent emetogenic drugs, and there is no reason to assume a priori that if THC is effective in other settings, that it should be effective against Adriamycin and Cytosan.

Finally, the antiemetic was given only 1 hour prior to chemotherapy. This is later than in most other studies and may not have allowed adequate absorption of drug at the peak of emetogenic activity. THC is erratically absorbed in any event, and blood levels in this study were low. It might simply be the case that THC was not given an adequate "chance" to work.

In any event, this must be considered a negative study in this selected population.

One final comment is in order. The sponsor has combined the results of the methotrexate-treated patients with those of this group and found some statistically significant results. This is meaningless from a clinical point of view, and unacceptable. These are essentially separate studies and must stand alone on their respective merits.

Marinol - Summary and Conclusions

The evaluation of drugs designed to ameliorate the nausea and vomiting induced by cancer chemotherapy is hampered by multiple obstacles. Multiple study designs, different emetogenic stimuli, the subjective and perhaps arbitrary nature of the rating scales used, the use of active controls all contribute to a picture that can be confusing at best, and incomprehensible at worst. This submission contains data from 8 studies, and all the problems noted above (as well as others) appear.

Because designs varied widely in this submission, separate statistical analyses have been performed on each study, with no attempt to pool data. This is appropriate, since it would be meaningless (and wrong) to pool data derived from such disparate trials. Each study must be judged on its own merits, and a decision must be made on this basis.

Several issues that appear consistently in most (if not all) the studies deserve discussion.

One major issue is the high rate of ADRs. Essentially every study documents a very high rate of ADRs in patients receiving THC, as compared with either placebo or active control. I believe, however, that the weight generally given to ADRs in attempting to define an acceptable risk/benefit ratio for most drugs may be inappropriate in this setting, for a number of reasons.

First, this population is critically ill, suffering from two serious and sometimes debilitating illnesses (cancer, nausea and vomiting due to cancer treatment). We must expect (and allow) a higher rate of ADRs because a serious and often refractory condition is being treated. This is all the more important because the symptom being treated with THC is often so severe that the primary chemotherapy is interrupted or stopped. So, in this most unusual situation, the THC may potentially serve two purposes - alleviating the distressing nausea and vomiting, and allowing the primary problem (cancer) to be treated. Because the "stakes" are so high, because the potential benefit is so important, we must be willing to except a relatively high rate of ADRs.

Secondly, and very importantly, the ADRs have been shown to be self-limited in all cases, and always to recede without specific treatment. That is, though they occur frequently, and are often "unusual" and perhaps frightening, they pose no serious threat to health. If given with appropriate warning, assurance and observation, their effects, severity, and even occurrence, may be minimized. Should the effects prove intolerable, the drug may merely be stopped, without sequelae.

Third, the drug is intended for (and should be limited to) use in patients who have been refractory to other antiemetics. This "second-line" indication is given to medications that are known to have a high rate of ADRs, and serves to

limit the number of ADRs seen, by limiting the number of patients receiving the drug. This should be the case with THC.

The acceptance of a higher rate of ADRs than we might normally allow is predicated on the assumption of demonstrated efficacy for its indicated use. Here a few words are in order about the evidence offered in support of the sponsor's claim.

As mentioned earlier, these studies are not without problems. However, at least two are of sufficient quality to be considered pivotal and, in addition, supportive evidence is presented.

The [redacted] and Kluin-Nelemans studies are methodologically sound - each has a placebo control group treatment period, and in each the chemotherapeutic regimen (and hence emetogenic stimulus) is a constant. These factors greatly facilitate an unambiguous interpretation of the results. While vomiting (and nausea) was in general not eliminated in either study, the difference in the nausea and vomiting scores was statistically in favor of THC over placebo in every variable tested. These differences were also noted to be clinically meaningful, as noted in the individual reviews. Design flaws noted in each study were not considered fatal, and I take these studies to provide proof of efficacy of this drug for the proposed indication in the population.

There were three other studies that included a placebo control group. The [redacted] study was determined to be negative. This does not negate the potential efficacy of THC. If the study was methodologically sound, we could say that the evidence suggests that THC may not be effective against the nausea and vomiting induced by Adriamycin and Cytosan. This does not effect conclusions reached about THC in patients receiving other chemotherapies. The study was, however, different from most other studies in that THC was given only 1 hour prior to chemotherapy, which may not have permitted adequate time for absorption of drug. In any event, the study cannot, obviously, be used to support efficacy, though it need not necessarily be interpreted as a major blow against the drug.

The Frytak study utilized a placebo arm in addition to an active control. Here, a statistically significant difference was noted in the number of patients who had no nausea and vomiting (a clearly meaningful outcome) on THC as compared to placebo. In addition, a statistically significant difference in the number of dropouts due to vomiting was noted between THC and the other two groups of patients. This study was therefore considered supportive.

The last study to use a placebo group was the Levitt study, which compared three doses of THC with placebo, no treatment, and active control. A number of questions are raised by this study, which are unanswerable.

First, several of the rating scales used in this study were undefined (even qualitatively) for the five intermediate values of a seven-point scale. This poses obvious problems for the interpretation of the data. Also, there was a very high incidence of side effects in all groups. For instance, drowsiness occurred in approximately 70% of all groups; depression occurred in 41% of placebo patients (about twice that seen in the THC group). Anxiety was seen in half the placebo and control groups, a figure comparable to that seen in the THC-treated patients. These rates of ADRs make one wonder about either the ratings, and/or the specific population studied. While the study must, of course, be considered negative, questions must be raised about the meaningfulness of the data.

The remaining studies employed active controls, and exhibit the problems encountered in the interpretation of the data generated.

Two studies (Ungerleider, Schein) are crossover designs, and both used compazine as the active control. While the sponsor makes certain claims of superiority for THC over placebo in both of these studies, I believe that when re-analyzed using "tougher" assumptions, these studies, in general, fail to distinguish between treatments. Since we do not know the expected placebo response, we do not know if the response is due to placebo effect. However, as pointed out, the good control of nausea and vomiting is unlikely to be seen in so many patients and over so many chemotherapies as a result of placebo effect. Also, compazine is generally regarded as effective for controlling severe nausea and vomiting and if that assumption is granted, equivalent control by THC implies efficacy. Whether these studies have the power to distinguish between these treatments is unknown, since we do not know what (true) difference we expect to see. These studies were considered supportive.

Briefly, the question of dose of compazine should be discussed. If the dose of compazine used in these studies was inadequate, this would have biased the outcome. However, 10 mg qid is the recommended dose for severe nausea and vomiting, and this is the dose used in these active control studies.

The remaining two studies are "historical" control studies.

In one (Laszlo) patients were entered who had been refractory to previous antiemetics, but this information about previous response was gathered in a retrospective way and is suspect. If one accepts this data (and other assumptions) the drug can be shown to be useful, but this is evidence of the weakest kind.

The other (Ekert) study is basically a crossover in which everyone received active control first, but the data from this period was obtained prospectively, and hence is only a "historical" control study in a very limited sense. The results are positive, and therefore supportive, but the design of the study (period and sequence effects cannot be factored out) limits the categorization of the results.

Other problems occurred in most studies and created difficulties in evaluating results.

One of the most common problems in study designs was the use of multiple chemotherapy regimens with various strengths of emetogenic potential used in patients with multiple types of cancer. This heterogeneity made it impossible (in those studies that used this design) to make a judgment about the efficacy of THC as an antiemetic in regard to specific anti-cancer drugs, as most regimens did not occur frequently enough in any study to be able to reach such a conclusion. However, those studies which were supportive of THC's efficacy in such a population gave evidence that it (THC) is active as an antiemetic. The fact that we may not be able to pinpoint exactly against which chemotherapy it is active does not detract from its demonstrated activity. Of course, the two pivotal studies do control for emetogenic stimuli - it is one of the factors contributing to their being designated as pivotal.

A word should be said about the issue of blinding. Most studies were blinded (either single or double) but in general, I doubt that this is meaningful. The large incidence of essentially characteristic ADRs seen in THC-treated patients most likely destroyed the blind for all involved. It would have been equally difficult to have a blinded rater, as frequent ratings were necessary (not one isolated measurement at a specified time after drug as is often done when a blinded rater is used). Also, the subjectivity of the outcomes necessitated patient input, and they almost undoubtedly were unblinded. This is not ideal, but does not negate the findings.

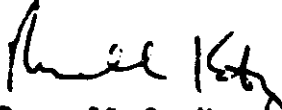
A critical recurrent problem was the method of observations used and the rating scales employed. Five studies looked at in-patients and ratings were done by nurses and/or patients. Both pivotal studies are included in this group. Two other studies (Ungerleider, Schein) utilized both in and outpatients, and one study (Frytak) utilized outpatients exclusively. In general, even in inpatient studies, patients' assessments were vital (nausea occurrence was always subjective, and even vomiting episodes were recorded by patients in-between checks by the nurses). Therefore, though I am inclined to place greater weight on data from inpatient studies, there is no reason to, a priori, dismiss results from other types.

The rating scales differed from study-to-study, though they basically measured the same variables. Since they were sometimes arbitrary (i.e., minimal vs. moderate nausea and/or vomiting) and almost always subjectively determined, most credence was given to results at the end points. That is, numbers of complete responders, severely nauseated patients, etc. Since number of vomiting episodes was more objectively determined, statistically significant differences in the parameter between THC and placebo treated patients could be determined and evaluated more clearly from a clinical point of view. That is, four episodes are clearly better than 10 or 15 episodes.

Because this condition is so severe and has such important consequences, I believe a favorable risk/benefit judgment can be made on the basis of the evidence presented here, even though it is not overwhelmingly positive. However, a few points will have to be addressed in the labeling.

1. The drug must only be use in patients refractory to other standard antiemetics. The evidence on efficacy does not unambiguously prove THC is better than compazine, but it does prove that the risk of ADRs is significantly higher.
2. Chronic treatment is not addressed on this submission. Most patients were treated with THC for one day; some were treated for several days separated by one or several weeks, and some of the evidence suggests that patients may become refractory to it after awhile. Nor, to my knowledge, has chronic toxicity testing been performed.
3. The maximum dose should probably be 15 mg THC, as the incidence of side effects is even higher at higher doses and the efficacy may not be increased.
4. In general, the drug should only be given to patients who can be observed, either in hospital or at home with a responsible party. The side effects can be frightening and patients should not be alone while under the drug's influence.
5. There is some evidence that elderly patients may have a higher rate of unpleasant side effects, and this may need to be taken into account.

With these provisions, I believe that Marinol can be approved as an effective antiemetic in those patients refractory to standard antiemetics with nausea and vomiting reduced by cancer chemotherapy.


Russell G. Katz, M.D.



Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

To :File NDA 18-651

From :Russell Katz, M.D. *Russell Katz*

APR 15 1985

Subject:Resubmission of Kluin-Nelemans Data and Designation of Schein
Study as an Adequate and Well Controlled Study Demonstrating Safety
and Efficacy

The original approvable letter sent to the firm on July 31, 1984 was rescinded
as a result of the findings of investigations

Because these transgressions were seen as very serious by the Agency, a
non-approvable letter was sent to the firm on November 5, 1984.

1. [redacted] would no longer be considered as part of the data
relied upon to determine safety and efficacy.

2. [redacted]
submitted. The Agency would accept this study as valid and determine
if it still demonstrated the safety and efficacy of Marinol.

The firm submitted the re-analyzed Kluin-Nelemans study on February 20, 1985.

Kluin-Nelemans

This was a double-blind, placebo controlled, counter balanced cross-over study in patients receiving MOPP therapy for Hodgkin's and non-Hodgkin's lymphoma. These patients were refractory to previously administered standard antiemetic therapy.

Patients: Twelve patients entered the trial, but only nine (9) received both treatments. There were ten (10) men and one (1) woman, and ages ranged from 20-53, with a mean age of 34.6 years.

Drug Schedules and Dosages: MOPP therapy was given in a 14 day cycle, in the following manner:

On days one and eight, patients received an IV infusion of chlormethine (6 mg/M², maximum 10 mg) and vincristine (1.4 mg/M², maximum 2 mg). In addition, patients received daily for 14 days oral procarbazine, 100 mg/M² and prednisone, 40 mg/M². Each patient received 6 cycles of MOPP.

Patients were randomly assigned to one of 4 sequence groups of THC-placebo treatment, consisting of three chemotherapy cycles each. During each cycle, patients were given antiemetic treatment on days one and eight. The anti-emetic was given 2 hours prior to chemotherapy and then at 4 and 8 hours later. The dose of THC was 10 mg/M².

Efficacy Variables: Patients were asked to rate their responses to study drug according to the following scale, in which their responses were compared to previous anti-emetic treatment:

1. No improvement, no change compared to former courses
2. Some improvement, vomiting and nausea of shorter duration or less vehement
3. Pronounced improvement, although still vomiting and nausea
- 4A. Very clear improvement, no vomiting but still nauseated
- 4B. Very clear improvement, no nausea, but still vomiting
5. Complete improvement, no nausea, no vomiting

These self-ratings were made at the end of days 1 and 8.

Analysis: The firm used data from the first periods that the patient received THC and Placebo. Data from days 1 and 8 were summed, and the Mann-Whitney U statistic was calculated for this 2 period cross-over trial. However, this study enrolled too few patients to test the assumptions necessary to analyze it as a cross-over study. Therefore, separate analyses were performed (see Results Section).

Results-Adverse Reactions:

THC: Eleven patients reported dizziness. Ten (10) experienced being "high". Two (2) patients discontinued the study because of dysphoric reactions. One (1) patient discontinued after one capsule of THC, when she became pale, stuporous, and anxious. It was later determined that this patient had had similar reactions unrelated to treatment with Marinol prior to this study which might have been functional. A total of 6/11 patients experienced dysphoric reactions, including fear and anxiety in 5 patients, time distortion in 4 patients, and hallucinations in 3 patients. Nine (9) patients became somnolent, while 3 experienced ataxia, 3 headache, and 3 parasthesiae.

Placebo: While receiving placebo, 2/9 patients had headache and 1/9 had difficulty concentrating.

Efficacy: Five (5) patients received drug in THC-Pbo order, 4 in Pbo-THC sequence. When summing scores for Days 1 and 8, the firm obtained totals of 52 for THC and 22 for Pbo. Means were calculated as 2.9 for THC and 1.2 for Pbo, with a P value of .016 in favor of THC. No period or sequence effects were noted.

As noted earlier, however, there were too few patients in this study to be able to test the assumptions on which an analysis of this study as a cross-over are based. Therefore, it is reasonable to analyze the study as a single period parallel study, only employing first period data. When this is done, combining scores on Days 1 and 8, the following results are obtained:

THC: [REDACTED] Mean 2.5

Pbo: [REDACTED] Mean 1

This difference reflects a clinically significant difference in response. In particular, it is seen that no patient who received Placebo scored higher than 1 on either day 1 or day 8, while patients who received THC in the first period all had at least some, and usually significant, improvement (see sponsor's Table 5).

If one analyzes the data for Days 1 and 8 separately, again employing only first period data, the following results are obtained:

	Means	
	<u>THC</u>	<u>Pbo</u>
Day 1	1.8	1
Day 8	3.2	1

Again, significant differences are noted, particularly on Day 8.

If the data are analyzed as cross-over data (that is, assuming that there are no carry-over effects), the results are as follows:

	Means	
	<u>THC</u>	<u>Pbo</u>
Day 1	2	1
Day 8	3.8	1.4

Here again, the results are at least as impressive as when analyzed as a single period parallel study.

Comments: As expected, there was a very high incidence of adverse reactions in this study, some of which were quite disturbing. However, they were all transient, and none required specific intervention. The reaction that caused one patient to withdraw after a single dose of THC could not reliably be attributed to drug. Therefore, despite the high rate of ADRs in this study, their transient and self-limited nature would make this acceptable if the drug is seen to be efficacious.

As the separate efficacy analyses show, THC invariably beat Pbo according to the judgements of the patients. In fact, of the 18 scores on Placebo (nine patients receiving Pbo on Days 1 and 8), only 2 were greater than 1 (see Sponsor's Table 5). Of the 18 scores on THC, 15 were greater than 1.

Therefore, independent of analysis, it is clear that THC performed clinically significantly superiorly to Placebo (also, see statistical review of April 11, 1985).

Several points remain to be discussed briefly.

First, it could be noted that these were patients who had, in general, failed to respond to available anti-emetics in the past, and therefore would not be expected to respond to Pbo. However, since THC will be approved for only those patients who have failed on other anti-emetics, this is the appropriate population to test.

Next, the scale appears rather subjective, in particular at the low end (1 and 2), and relies on patients' memories regarding prior responses. This is true, though not necessarily a drawback. Many scales used to gauge response to drug treatment require a subjective response on the part of the patient, and there is no a priori reason to assume that such a scale will yield results biased in one direction or the other.

Finally, the scale does not allow for the possibility that either of the treatments could have been worse than previous treatments. Theoretically, at least, it is possible that patients did worse on THC as compared to Pbo (when judged against previous anti-emetic response), yet this would not have been picked up. However, there is no reason to believe that this was the case, particularly since only 3 times did patients rate THC as 1, thereby allowing the possibility that such was the case only very infrequently, whereas the possibility that Pbo was worse than previous treatments occurred 16/18 times.

I believe this is an adequate and well controlled study demonstrating the safety and efficacy of THC in the treatment of the nausea and vomiting associated with cancer chemotherapy.

In addition, the Schein study, reviewed below, is considered a second adequate and well controlled study demonstrating the efficacy of Marinol.

SCHEIN STUDY

This is a double-blind crossover study comparing THC with compazine. It was originally designed as a four-period crossover study. However, the study was analyzed as a parallel group study using only first period data.

Patients - Thirty-two (32) patients with 12 types of cancer and 26 different single or combination chemotherapy regimens were included. There were 23 females, 9 males, and 29 outpatients and 3 inpatients.

Drug Schedules and Dosages

Patients took the study antiemetic 1 hour prior to chemotherapy and every 4 hours thereafter for no more than 48 hours after the start of the chemotherapy. The doses of antiemetics were:

THC - 15 mg/M²
Compazine - 10 mg

Efficacy Variables

1. Severity of Nausea

- 0 - none
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - incapacitating

2. Duration of Nausea

The total duration of nausea during each treatment.

3. Severity of Vomiting

- 0 - none
- 1 - mild
- 2 - moderate
- 3 - severe
- 4 - incapacitating

4. Number of Vomiting Episodes

Calculated by multiplying the frequency/hour by the duration of observations.

5. Patient's Evaluation

Patients were asked to select which treatment was best (if any).

6. Investigator's Global Evaluation - classified as follows:

- a. Complete responder - no vomiting and no, or slight, nausea
- b. Partial responder - moderate vomiting and/or nausea
- c. Poor responder - severe vomiting and/or nausea.

7. Final Outcome - Patients were classified as to whether they completed at least one course of each study drug.

Observations - Patients recorded in a diary the ratings described above. There was one score for variables 1 and 3 for each observation period.

Results - Adverse Reactions

All 32 patients who took THC had a side effect of some sort. Eight (8) (25%) had a "high". Eight (25%) also experienced dizziness, and 8 were drowsy. Nine patients (28%) were weak, had an unsteady gait, or were otherwise unable to move. Four patients (12%) were confused and disoriented. Six (19%) had visual distortions or double vision; 3 patients had hallucinations, and 4 (12%) were paranoid. Fifteen patients (47%) had dysphoric reactions, and 14 (44%) had other unpleasant reactions. Three patients (9%) had a pleasant experience only. Twelve patients (12) discontinued the study due to THC side effects.

Only 2/21 (9%) patients had adverse reactions on compazine. Each felt drowsy, and 1 in addition had a "drugged" feeling.

Efficacy

Eighteen (18) patients received THC first; 14 received compazine first. Only 7/18 (38.9%) who took THC first crossed over to compazine. All patients who took compazine first crossed over to THC. This was significant at the .001 level. Six of the 11 who did not cross over did so due to severe side effects of THC. Two discontinued because they got no relief from THC; the remaining 3 discontinued for reasons that are unclear.

Because of the large number of dropouts in this study, only first period data were analyzed. Results of the analysis of the primary efficacy variables using Wilcoxon Rank Sum tests are given below.

<u>Variable</u>	<u>P-Value (2 tail)</u>
Nausea Severity	.17
Nausea Duration	.30
Vomiting Severity	.04
Vomiting Episodes	.02

Raw data are found in Sponsor's Table 9.

Comments - Adverse Reactions

The incidence of side effects was obviously high, as all patients who took THC had reactions to it. The usual ADRs were noted, but a relatively high rate of dysphoric reactions (47%) was seen. This is possibly because the dose of THC used in this study was large - 15 mg/M². The high rate of this severe reaction provides useful safety information about acceptable dose ranges of THC. Again, though, the reactions, while severe in certain cases, were all self-limited and temporary, requiring no specific medical intervention. If the data demonstrate efficacy, the occurrence of these ADRs should not preclude a positive assessment of the risk-benefit ratio.

Efficacy

An analysis of this study as a cross-over would be confounded by the large number of dropouts. Therefore, it is appropriate to use first period data only, and treat the study as a simple parallel group trial.

When this is done, it is clear that statistically and clinically meaningful differences exist between Marinol and Compazine regarding the control of vomiting in this population. Indeed, the one reasonably objective variable, # of vomiting episodes, is most positively affected by Marinol. This is particularly persuasive, given that Marinol has been shown to be superior to an active control. Regarding nausea, the differences directionally favored Marinol, though they did not reach statistical significance. This speaks to the comparability of the two treatments with regard to this variable.

This outcome is acceptable as evidence of the effectiveness of Marinol. Even given the limitations inherent in drawing conclusions from a finding of no difference between drug and active control on the nausea variables (e.g., issues of power, assumptions about the efficacy of the standard, etc.) the results allow a definitive conclusion to be drawn regarding the control of vomiting. This result not only makes sense from a clinical point of view (that is, in those cases where nausea and vomiting form a continuum of symptoms, one might expect to see vomiting affected before nausea as opposed to the other order), but it is clearly clinically useful. One would not necessarily require of a drug that it have a significant effect on nausea if it had such an effect on vomiting. That is, obviously, vomiting is by itself a symptom worth treating.

The difference in chemotherapy regimens that patients received should be discussed. There is no way that the emetogenic potential of these regimens can be controlled for, or adjusted for, in the analysis. This is potentially a problem in particular when the study is regarded as a single period trial. However, there is no reason to assume that there was a significant incomparability of emetogenic stimuli at baseline in the two groups. In addition, the positive effect seen across multiple chemotherapeutic regimens lends support to the notion that Marinol is effective in general against vomiting induced by chemotherapy, not just against the vomiting induced by a specific chemotherapeutic agent.

Therefore, the Schein study is acceptable as an adequate and well controlled study demonstrating the safety and efficacy of Marinol for use in the treatment of the nausea and vomiting associated with cancer chemotherapy.



TABLE 5
CHRONOLOGY OF PATIENT IMPROVEMENT SCORES
ACCORDING TO DRUG SEQUENCE

N = 11 Patients	1st Chemo Cycle Improvement Scores		2nd Chemo Cycle Improvement Scores		3rd Chemo Cycle Improvement Scores		Sum of Day 1 and 8 Scores for Data Utilized in Crossover Analysis
	Day 1 Course	Day 8 Course	Day 1 Course	Day 8 Course	Day 1 Course	Day 8 Course	
THC-Placebo-THC Sequence	1 4A 1 1	2 5 2 5*	1 1 1 1	1 1 1 ②	THC 4-5 5 1 Not Done	THC 4-5 5 1 Not Done	3 9 3 6
Placebo-THC-Placebo Sequence	1 1 1	1 1 1	2 3 2	4A 5 4B	Placebo 2 1 2	Placebo 2 1 2	6 8 6
THC-THC-Placebo Sequence	2	(2**)	2	5	1 3*** 1	④A 3***	4 5
Placebo-THC-THC Sequence	1	1	2	5	THC 3	THC 3	7 2
THC - No Cross-Over	2 Not Done 4A No scores						52 22
					Totals		
					Mean b		2.9 1.2

a Utilized in cross-over analysis
b Mean Score: Total - (2 x 9)

* Score was 4A in published report
** Score was 4B in published report
*** Score was 5 in published report
**** THC taken instead of placebo

Scale:

1 = No improvement, no change compared to former courses
2 = Some improvement, vomiting and nausea of shorter duration or less vehement
3 = Pronounced improvement, although still vomiting and nausea
4A = Very clear improvement, no vomiting, but still nauseated
4B = Very clear improvement, no nausea, but still vomiting
5 = Complete improvement, no nausea, no vomiting

NDA 18651

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NDA 18-651

Unimed Incorporated
Attention: Mr. Paul Bolenbaker
35 Columbia Road
Somerville, New Jersey 08876

Dear Mr. Bolenbaker:

Please refer to your new drug application dated June 24, 1981 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation MARINOL (ironabtinol; delta-9-tetrahydrocannabinol) capsules.

We also acknowledge receipt of your additional communications dated November 23, 1984 and February 20, 1985. Additionally, we refer to your amendment dated August 17, 1984; to our approvable letter dated July 31, 1984; and to our not approvable letter dated November 5, 1984.

We have evaluated the explanations offered by your firm for the discrepancies discovered in your original application that caused us to rescind our approvable letter of July 31, 1984. We have concluded that the inaccurate and misleading representation of the results of two studies in your application was not purposeful, but arose as a consequence of the desire of your staff to satisfy what they believed to be FDA requirements. Nonetheless, while we believe that your staff did not intend to deceive us, we remain disturbed that the studies could have been represented as they were. As we have discussed during the post-marketing period, a sponsor has major responsibilities for reviewing and evaluating new adverse drug reaction information, and for developing revised labeling information if needed. We acknowledge your commitment to accept personal responsibility to ensure that any post-marketing surveillance is conscientiously and competently carried out.

We have completed our review of your revised application (submitted in two parts: August 17, 1984 and February 20, 1985) and have concluded that the data, including the revisions submitted in response to our letter of November 5, 1984, demonstrate the safety and efficacy of dronabinol for the treatment of nausea and vomiting associated with cancer chemotherapy. Your application is, therefore, considered 'approvable.'

However, before approval can be granted, extensive revision of the submitted draft labeling is required. The revised labeling should be presented in final format. (However, we recommend that the number of copies of labeling printed be limited because additional revisions may be required prior to final approval.)

The labeling should follow the outline provided below. In instances where we propose specific wording, please use the text verbatim. In instances where we ask that you make specific corrections, please include the appropriate changes. Because dronabinol is a controlled substance, all labeling must display a scheduling symbol (i.e., C-II) as required by 21 CFR 1302.

Proposed Labeling:

MARINOL Package Insert

MARINOL
(Dronabinol)

DESCRIPTION:

MARINOL brand of dronabinol (delta-9-tetrahydrocannabinol, THC), [(6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol] is the principal psychoactive substance present in *Cannabis sativa* L. (marijuana). It has the empirical formula $C_{21}H_{30}O_2$ with the molecular weight of 314.45. It has the following structural formula:

[NOTE TO FIRM: PLACE STRUCTURAL FORMULA HERE AS IN YOUR SUBMITTED LABELING]

MARINOL is chemically synthesized and formulated in sesame oil and encapsulated in round soft gelatin capsules for oral administration.

CLINICAL PHARMACOLOGY:

Non-therapeutic Effects:

Dronabinol, commonly known as delta-9-THC, is one of the major active substances in marijuana. For practical purposes, the non-therapeutic effects of dronabinol may be considered essentially identical to those of marijuana and other centrally active cannabinoids. MARINOL is highly abusable and can produce both physical and psychological dependence.

Dronabinol has complex effects upon the central nervous system. Subjects using cannabis may 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 latter phenomena appear to be more common when larger doses of dronabinol 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.

Reliable information on the behavioral effects of chronic dronabinol use is not available; however, it has been reported that chronic use of cannabls may be associated with decrements in motivation, cognition, judgment, etc. (Whether these impairments reflect the underlying character of individuals chronically abusing cannabls or are a result of the use of cannabls is not known.)

Dronabinol, used within or slightly above the recommended dose range, has several systemic effects of interest. It characteristically causes an increase in heart rate and conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or fainting upon standing. In one study, a slight but consistent decrease in oral temperature was recorded.

The potential of dronabinol to cause tolerance and physical dependence was examined in a 30 day rising dose tolerance study. Following thirty days of use, tolerance developed to the cardiovascular and subjective effects of dronabinol administered at doses up to 210 mg/day. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A fall in supine blood pressure, made worse by standing, was also observed initially. Within days, however, these effects disappeared, indicating the development of tolerance.

A withdrawal syndrome, consisting of irritability, insomnia, and restlessness, was observed in some subjects within 12 hours following abrupt withdrawal of dronabinol. The syndrome reached its peak intensity at 24 hours when subjects exhibited "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs and anorexia. The syndrome was essentially complete within 96 hours. Electroencephalographic changes recorded following dronabinol discontinuation were consistent with a withdrawal syndrome. While on drug, dronabinol produced a decrease in REM sleep. Following discontinuation, a marked rebound of REM sleep occurred. Several subjects reported impressions of disturbed sleep for several weeks after discontinuing high dose dronabinol. Dronabinol is not an oploid, and does not cause oploid-like effects upon respiration or pupil size.

Metabolism and Pharmacokinetics:

Reliable information on the pharmacokinetics of MARINOL are not yet available. The following summary highlights important aspects of the literature concerning the absorption, distribution, metabolism and elimination of dronabinol; however, differences in the preparation, formulation and method of administration make it difficult to extrapolate this information directly to the drug product, MARINOL.

Following oral administration, dronabinol has a systemic availability of 10 to 20% relative to an I.V. dose, indicating that the drug undergoes extensive first pass metabolism. Numerous metabolites have been identified, including 11-hydroxy-tetrahydrocannabinol, which is psychoactive. Dronabinol has a volume of distribution about 100 times as large as the plasma volume.

MARINOL is contraindicated in any patient known to be hypersensitive to either dronabinol or sesame oil.

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

CONTRAINDICATIONS:

Evidence supporting the efficacy of MARINOL in the treatment of nausea and vomiting induced by cancer chemotherapy was obtained from a variety of sources. The most persuasive evidence was obtained in subjects being treated with MOPP for Hodgkin's and non-Hodgkin's lymphomas. Other evidence supports the conclusion that MARINOL is effective against nausea and vomiting induced by other cancer chemotherapy regimens employed in the treatment of a wide variety of tumor types.

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

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

MARINOL is 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 patients treated with MARINOL can be expected to experience disturbing psychotomimetic reactions not observed with other antiemetic agents.

INDICATIONS AND USAGE:

The maximum plasma concentrations of dronabinol, the 11-hydroxy metabolite, and several other metabolites occur approximately 2 to 3 hours after oral dosing. Biliary excretion is the major route of elimination. Within 72 hours following oral administration, approximately 50% of the dose is recovered in feces; another ten to fifteen percent appears in the urine either unchanged or as a metabolite. Renal clearance in normals is approximately one-tenth of the glomerular filtration rate.

The elimination phase of dronabinol exhibits biphasic kinetics with an alpha half-life of about 4 hours and a terminal half-life of 25 to 36 hours. The principle active metabolite, 11-OH-delta-9-THC, appears in the plasma in roughly the same mg quantities as its parent. The terminal plasma half-life for the 11-OH-delta-9-THC is approximately 15-18 hours. Thus, extended use of MARINOL at the doses recommended in this labeling may cause the accumulation of toxic amounts of dronabinol and its metabolites.

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 MARINOL. The effects of MARINOL may persist for a variable and unpredictable period of time following its oral administration. Dronabinol is highly lipid soluble and it and its metabolites may persist in tissues, including plasma, for days. Because of individual variation in response and tolerance to the effects of MARINOL, the physician should determine on clinical grounds the period of patient supervision required. Patients receiving MARINOL 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 MARINOL (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 MARINOL 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 MARINOL until he/she has been examined, and the circumstances evaluated, by a physician. If the clinical situation warrants it, a lower dose of MARINOL 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 MARINOL.

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

PRECAUTIONS:

Because it may cause a general increase in central sympathomimetic activity, MARINOL should be used with caution in persons with hypertension or heart disease. MARINOL should be used cautiously in manic, depressive, or schizophrenic patients as the symptoms of these disease states may be unmasked by the use of cannabinoids.

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

Information for patients:

Persons taking MARINOL should be alerted to the additive central nervous system depression resulting from simultaneous use of MARINOL and alcohol or barbiturates. This combination should be avoided. Operation of machinery or a motor vehicle should be avoided during MARINOL therapy. Patients using MARINOL 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 MARINOL.

WARNINGS:

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In controlled clinical trials, the most frequently reported adverse reactions involved the central nervous system. In decreasing order of frequency these events were drowsiness, muddled thinking and brief impairment of coordination, sensory and perceptual functions. Easy laughing, elation and heightened awareness, often termed a "high", was observed in 24% of MARINOL patients.

ADVERSE REACTIONS:

MARINOL is concentrated and secreted in human milk and is absorbed by the nursing baby. Because the effects on the infant of chronic exposure to MARINOL and its metabolites are unknown, nursing mothers should not use MARINOL.

Nursing Mothers:

Reproduction studies have been performed in mice, rats and rabbits at doses up to 400 times, 32 times, and 10 times the human dose respectively and have revealed no evidence of teratogenicity due to MARINOL. At these dose levels in mice and rats, which produced substantial reductions in maternal weight gain, MARINOL caused a decrease in the number of viable pups, an increase in fetal mortality and an increase in early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are, however, 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.

Pregnancy:

Reproductive studies have not been performed with MARINOL. Reproductive studies in mice (approximately 32-400 times the human dose) and rats (approximately 8-32 times the human dose) demonstrate that MARINOL causes a decrease in pregnancy rate. In a long term rat study (77 days), oral administration of MARINOL at doses 3-17 times the human dose reduced ventral prostate, seminal vesicle and epididymal weights and caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of developing germ cells, and number of Leydig cells in the testis were also observed. However, sperm count, mating success and testosterone levels were not affected. The significance of these animal findings in humans is not known.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

The effects of MARINOL on blood ethanol levels are complex. During sub-chronic MARINOL administration (60 mg/day) for ten days, absorption of ethanol was delayed, resulting in lower and delayed peak blood alcohol levels. Metabolism of ethanol was increased in some subjects and decreased in others. The overall rate of ethanol disappearance was decreased by about ten percent.

Drug Interactions:

The incidences listed in the following table are derived from comparative double-blind, crossover or parallel design trials in which patients received MARINOL, an active control drug (usually prochlorperazine) or placebo. 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 often differ from those which obtained in the clinical trials. Furthermore, these figures should not be compared with those obtained in other clinical studies involving related drug products and placebo, as each group of drug trials are conducted under a different set of conditions.

FREQUENCY OF ADVERSE EFFECTS FROM CONTROLLED STUDIES

Body System/ Adverse Reaction	MARINOL (n=317)	Control (n=263)	Placebo (n=68)

CENTRAL NERVOUS SYSTEM:			
Drowsiness	48	33	49
Dizziness	21	5	1
Muddled Thinking	12	1	1
Perceptual Difficulties	11	1	0
Anxiety	16	3	24
Coordination Impairment	9	2	10
Irritability/weird feeling	7	3	0
Depression	7	3	15
Weak, sluggish	6	3	1
Headache	6	4	4
Hallucinations	5	0	0
Memory lapse	5	1	0
Unsteadiness, ataxia	4	1	0
Paranoia	2	0	0
Disorientation, confusion	1	0	2
Depersonalization	2	0	0
AUTONOMIC NERVOUS SYSTEM:			
Dry mouth	3	1	1
Paresthesia	3	0	1
Visual distortions	3	0	0
CARDIOVASCULAR:			
Tachycardia	1	1	0
Postural hypotension	1	0	0

In addition to the events enumerated above, the following have been reported at a frequency below one percent: CENTRAL NERVOUS SYSTEM: tinnitus, nightmares; AUTONOMIC NERVOUS SYSTEM: speech difficulty, facial flushing, perspiring; CARDIOVASCULAR: syncope; GASTROINTESTINAL: diarrhea, fecal incontinence; MUSCULOSKELETAL: muscular pains.

DRUG ABUSE AND DEPENDENCE:

MARINOL is highly abusable and controlled as delta-9-tetrahydrocannabinol under schedule II of the Controlled Substances Act. Prescriptions of MARINOL should be limited to the amount necessary for a single cycle of chemotherapy (i.e., a few days).

No cases of overdosage in multiples of prescribed dosages were reported in the controlled clinical studies. Few deaths have been reported from the use of dronabinol in any of its many forms (e.g., hashish, marihuana, etc.). Two incidents of death following the ingestion of large overdoses of Indian Hemp have been reported, while one death resulting from smoking cannabis herb and/or resin has appeared. No estimate of actual dosage was provided in either case. However, from a case of severe coma due to cannabis in a young French soldier, who recovered with conventional supportive therapy (intubation, I.V. fluids), it has been estimated that the acute lethal intravenous dose of dronabinol would be on the order of 1000 - 2000 mg total dose. Although this is a crude extrapolation at best, it represents a five-

Overdosage at Multiples of Prescribed Dosages:

Particular attention should be paid to the vital signs in these patients, as tachycardia and both hyper- and hypotension are common adverse reactions. These signs should be monitored and treated if necessary in the usual manner according to the judgment of the physician.

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 the patient has 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 24 hours without specific medical therapy.

Overdosage at Prescribed Dosages:

Signs and symptoms of overdosage are an extension of the psychotomimetic and physiologic effects of MARINOL, 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, non-therapeutic, doses.

OVERDOSAGE:

It is not known what proportion of individuals exposed chronically to MARINOL or other cannabinoids will develop either psychological or physical dependence. Long term use of these compounds has 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 delta-9-THC (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.

to ten-fold multiple of the maximum oral dose recommended for MARINOL in a twenty-four period.

DOSAGE AND ADMINISTRATION:

MARINOL is best administered at an initial dose of 5 mg/M², given 1-3 hours prior to the administration of chemotherapy, then every 2-4 hours after chemotherapy is given, for a total of 4-6 doses/day. Should the 5 mg/M² dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/M² increments to a maximum of 15 mg/M² per dose. Caution should be exercised, however, as the incidence of disturbing psychiatric symptoms increases significantly at this maximum dose.

HOW SUPPLIED:

MARINOL (dronabinol solution in capsules),
2.5 mg; bottles of 50; Imprint UNI-1 (white);
NDC 0051- [NOTE TO FIRM: Please insert the actual NDC number assigned into the final printed labeling]

MARINOL (dronabinol solution in capsules),
5.0 mg; bottles of 50; Imprint UNI-2 (dark brown);
NDC 0051- [NOTE TO FIRM: Please insert the actual NDC number assigned into the final printed labeling]

MARINOL (dronabinol solution in capsules),
10.0 mg; bottles of 50; Imprint UNI-3 (orange);
NDC 0051- [NOTE TO FIRM: Please insert the actual NDC number assigned into the final printed labeling]

MARINOL capsules should be preserved in a well sealed container, and stored preferably under refrigeration (8° - 15° C) for optimal stability.

END DRAFT LABEL

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.

Please submit a "safety update" containing reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference from the previous reports in the rate of occurrence of common, but less serious, adverse events. 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.

We note your commitment, as communicated in your amendment dated August 17, 1984, to perform the three biopharmaceutical studies requested in our letter of July 31, 1984. Additionally, we concur with your explanation regarding the

suitability of your selected tradename "MARINOL" and the unlikelihood of its confusion in clinical practice.

We request that you submit updated copies of the introductory promotional material which is proposed for this product, to include the revised labeling as discussed above. Copies should be submitted with a cover letter to both the Medical Review Division and the Director, Division of Drug Advertising and Labeling (HFN-244). Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission. This form is for routine use, not proposed materials.

Please submit twelve copies of the final 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,

Robert Temple, M.D.

Director

Office of Drug Research and Review

Center for Drugs and Biologics

cc: Orig. NDA

NYK-DO

HFN-85

HFN-226/PHEPP

HFN-713/RSTEIN

HFN-100/RTemple

HFN-120

HFN-120/SBium/Rshultz

HFN-120/Glin/JContera

HFN-120/Fvocci/ETocus

HFN-120/RKatz

HFN-120/RNighswander/Plieber

draft;rnighswander/3/21;25/85

edit;rkatz/3/21/85

edit;plieber/3/26;4/16/85

DOC # 3553p (from 0193x)

Statistical Review and Evaluation

NDA #: 18-651/Drug Class: 1C

APR 11 1985

Applicant: Unimed, Inc.

Name of Drug: Marinol (delta-9 tetrahydrocannabinol)

Documents Reviewed: Volume 7.1 dated 2/20/85

The reviewing medical officer for this submission is Russell Katz, M.D.,
HFN-120.

1. Background

Marinol was previously reviewed by the Division of Biometrics in documents dated 4/18/84 and 10/2/81. The purpose of the present submission is to analyze the original data of Dr. Kluin-Nelmanns. This original data has not been reviewed to date by FDA.

2. Applicant's Analysis and Results

The applicant analyzed statistically the patient improvement scores. According to Dr. Katz, this is the appropriate variable to consider. The applicant considered the 9 patients with complete crossover data for days 1 and 8. Thus data for one patient with only period 1 data and the data for a second patient who had data for only day 1 of period 1 were omitted.

The applicant summed the within period day 1 and day 8 improvement scores and analyzed the result using Koch's non-parametric method of analysis. A treatment effect was found at the 2-tail $p=0.02$ level. No statistically significant differences were found for period or residual effects ($p > .19$).

3. Reviewer's Comments

The applicant's analysis is correct if it is assumed that (a) there is no difference in treatment effect between day 1 and day 8, (b) the p-value for residual effects shows that residual drug effects are not present upon crossover, (c) the placebo data for patient #4 are the same as if that patient had received D9THC for 1 week followed by 1 week of placebo treatment without an extra week of D9THC between the periods. With so little data available, the validity of these assumptions is difficult to evaluate.

For this reason, I have performed six more statistical analyses of these data tabulated in section 4 of this review.

4. Reviewer's Statistical Analyses and Results

Like the applicant, I will consider the investigator's assessment of improvement. Four separate statistical analyses will be performed considering the day 1 and the day 8 data separately, assuming first that residual effects are present, and then assuming that residual effects are not present. Two additional analyses were done using the applicant's method of statistical analysis. These analyses require the assumption that it is valid to combine the day 1 and day 8 data. The only difference between my analysis and the applicant's is that I have omitted the data for patient #4 mentioned in section (3).

I have analyzed the first period data of all patients on an "intent-to-treat" basis using a Wilcoxon Rank Sum test when it is assumed that a residual effect was present. When it is assumed that no residual effect was present, I performed Koch's non-parametric analysis of the crossover design at day 1 and at day 8 for the same set of patients considered by the applicant less the patient in the sequence D9THC-D9THC-Pbo.

The following table is similar to that in my review of 4/18/84, and gives the results of the analyses just described.

TABLE 1: FDA Reviewer's Findings

Treatment Group Residual Effects	2-tail p-values for Treatment Effect	Exist(1)	Don't Exist(2)
Day 1	.08	.02	
Day 8	.01	.02	
Day 1 and 8 averaged	.01	.02	

(1) First period data analyzed using Wilcoxon Rank Sum test.
 (2) Crossover data analyzed using Koch's (1972) method.

5. Conclusion

At worst, there is marginal statistical evidence that Marinol is effective. It requires medical judgement to make a weighted evaluation of Table 1.

Richard A. Stein

Richard A. Stein, Ph.D.
 Mathematical Statistician

Statistical Review and Evaluation

Date: OCT 2 1981

NDA#: 18-651/Class 1C

Applicant: UNIMED inc.

Drug Name: Marinol (delta-9-tetrahydrocannabinol; D9THC)

Documents Reviewed: Volumes 1.1, 1.2, 1.8-1.13 dated 6/25/81 by FDA

This review involved clinical input from John Johnson, M.D., HFD-150, who accepts these findings.

1. Background and Summary

Current available anti-emetics used in conjunction with cancer chemotherapy usually do not control nausea and vomiting effectively or consistently. Delta-9-tetrahydrocannabinol (D9THC) is a class 1C drug proposed by the applicant for this purpose. The applicant's labeling is clear and concise. "Tetrahydrocannabinol capsules are solely indicated for the prevention and treatment of nausea and vomiting due to the use of certain toxic anticancer agents. They may not be used otherwise." The National Cancer Institute presently handles the distribution of tetrahydrocannabinol to needy patients. There is some statistical evidence to support the applicant's efficacy claim, but on balance it is not sufficiently strong for one to draw definitive conclusions concerning D9THC for the following reasons:

- (1) The studies of Chang using methotrexate on 15 patients and of Kluhn-Nelms using 9 patients on MOPP therapy are statistically positive, but they are small in size.
- (2) The Frytak study is, at best, marginally positive to demonstrate the effectiveness of D9THC on statistical grounds.
- (3) Statistical analysis cannot extrapolate reliably the results of the Ekert and Laszlo historical control studies to those obtainable from a double-blind, randomized, concurrently controlled clinical trial.
- (4) The studies of Ungerleider, Schein, and Levitt were by design, uncontrolled, except through randomization, for strength of emetic stimulus. The applicant's analysis ignores without justification, differences in strength of emetic stimulus between patients in the treatment groups. However, based on information obtained from Dr. Johnson, this reviewer believes that a post-hoc adjustment of the

statistical analyses for strength of emetic stimulus after the completion of these studies, could lead to more distortion of the results than might be present without such an adjustment,

Finally, this reviewer believes that there is no valid way to combine statistically the evidence from these clinical trials to obtain a more definitive assessment of the efficacy of D9THC.

2. Study Characteristics

Eight investigators involving a total of about 520 patients studied the anti-emetic potential of D9THC under protocols which, in the applicant's words differed in their detail. Table 1 in the appendix displays design differences of statistical interest. Table 2 shows the various study variables used to evaluate efficacy and shows which specific scales each physician used. It is clear from Table 2 that the common study variables were the global evaluation of nausea and vomiting, the severity of nausea, and the severity of vomiting scales. The actual hedonic scales used varied among investigators.

The studies appear to cover a wide range of chemotherapy of varying emetic potential. Generally, patients were given an anti-emetic test drug between 1 and 2 hours before chemotherapy. Baseline measurements of the efficacy variables were made in the studies of Ungerleider, Kluin-Nelemans, Laszlo, and Ekerdt. The anti-emetic agent was re-administered in most studies about every four hours.

3. Applicant's Analyses

Demographic and background variables received no statistical analysis.

The key variables in the applicant's analyses were the global evaluation of nausea and vomiting, the assessment of nausea, the assessment of vomiting, the assessment of dropout rates, the assessment of sedation, pleasant, and unpleasant reactions. All these variables did not occur in each study.

The statistical techniques were quite diverse ranging from parametric t-tests, analyses of variance, and contingency tables, to Koch's non-parametric analyses of crossover study data. Such diversity is necessary since protocols varied widely and so did the variables measured in each study.

4. Reviewer's Comments

These comments supplement those directed to the applicant.

(A) The applicant states that protocol differences between the eight investigators are minor. To the statistician, this is not true. Some studies are crossover designs others have parallel groups, some are positive controlled, some are negative controlled, some are both, some

- have historical controls. To pool these studies for statistical analysis would be fruitless.
- (B) Each of the eight studies suffers from an important statistical omission. The applicant has not shown that his statistical analyses of these specific eight studies are not biased by differences between various patient groups obtained by randomization. If the results of these studies are taken at face value, the following points can be made.
- (a) In the concurrent placebo controlled trials of Chang, Kluin-Nellemans, Levitt, and Frytak only the 15 methotrexate patients in the Chang study and the 9 patients of the Kluin-Nellemans study give statistically positive evidence that D9THC is superior to placebo in counteracting nausea and vomiting.
- (b) The 116 patients of Frytak provide marginally positive evidence that D9THC is superior to placebo.
- (c) The 117 patients of Levitt and the 9 Adriamycin/Cytosin patients of Chang are of no value in showing D9THC superior on statistical grounds to placebo.
- (d) The studies of Schein and Ungersleider demonstrate no statistically significant difference between D9THC and Compazine in controlling nausea and vomiting.
- In summary, only the very small placebo controlled studies show statistically at the 5% significance level that D9THC is superior to placebo. The Frytak, Schein, and Ungersleider studies provide marginal evidence of the effectiveness of D9THC. The Levitt study and part of the Chang study provide no evidence of the effectiveness of D9THC. Finally, there is no statistically satisfactory way of combining the evidence of these studies to arrive at an overall decision about the effectiveness of D9THC.
- (C) It is not clear in this submission how the applicant made the association between any statistical analysis performed and his clinical conclusions.
- (D) The statistical analyses themselves are so vaguely specified that this reviewer feels that he often might not succeed in merely being able to duplicate the applicant's numerical results.
- (E) The "nausea" and "vomiting" scales are key to comparing the anti-emetic effectiveness of D9THC to other control drugs. Since the "global evaluation" scales are either exact or nearly exact functions of the nausea and vomiting scales, analyses of the global scale do not represent independent analyses.

- (F) The parametric ANOVAs performed on the "nausea and vomiting" scale can not be considered to have a reliable interpretation. This is because the basic data tabulated on pages 180 and 200 follow a U-shaped distribution.
- (G) The applicant's parametric analysis of nausea and vomiting is based on a variable called MD. The applicant does not explain how this variable is calculated and how missing values are treated.
- (H) This reviewer has performed in the Ungerleider study a cursory non-parametric analysis of the nausea and vomiting scale data for single course patients, multiple course patients and these patients combined. This analysis gives a result directionally favoring Compazine over D9THC which is not close to statistical significance ($p > .20$). The applicant's analysis showed the opposite trend, i.e., a result directionally favoring THC.
- (I) In the opinion of Dr. Johnson, HFD-150, the strength of the chemotherapeutic emetic stimulus can be expected to influence the ability of the anti-emetic drug to be effective. The Ungerleider study was a two period, two treatment crossover trial. Since different patients are allocated to the two sequence groups and since the sequence effect is estimated on the basis of the sum of the data over the two treatments within each sequence group, the sequence effect can be both due to differences in demographics not adequately controlled by the randomization and due to differences in the emetic potential of the chemotherapy given to each sequence group. Since baseline measurements are obtained before chemotherapy, the baseline subtraction performed by the applicant can not compensate for group differences. The sequence effect identified in the analysis of single course patients on page 178 may not be due to residual drug effects but rather to the factors just mentioned. Furthermore, why should multiple course patients not show a sequence effect? For this reason a statistical analysis for group differences in patient demographics and chemotherapy is important, if only to verify that these factors are not expected to bias conclusions.
- (J) In the Frytak study, the applicant claims no significant difference ($p > .13$) between the dropout rates of patients on D9THC, Compazine, and placebo (Vol. 1.2, page 381) using one of the procedures least likely to detect a difference should one exist. This reviewer finds a marginally significant difference between D9THC dropout rate of 34% and the placebo dropout rate of 16% ($p = .08$) using either the empirical logistic method of Cox or the Wilcoxon rank sum test. No statistically significant difference was found by this reviewer between the D9THC dropout rate of 34% and the Compazine dropout rate of 20% ($p = .14$).

- In the case of patients withdrawn from the study due to persistent vomiting, the applicant fails by his analysis, to show what this reviewer considers a statistically significant result favoring D9THC over Compazine (Vol. 1.2, page 382) at the 5% level and a marginal result favoring D9THC over placebo (p=.08).
- (K) The Ekert and Laszlo studies consist of only one sequence group of a two period crossover design and can not be properly evaluated statistically because the potential biasing effects of period and drug sequence cannot be estimated or accounted for. It is not possible for an analysis of patient demographics and therapy regimens to overcome these statistical drawbacks.
- (L) In the Levitt study, neither the applicant nor this reviewer could identify a dose-response relationship between the amount of D9THC administered and its ability to suppress nausea and vomiting. This raises two questions: (1) are there any dose related trends in demographic or emetic stimulus variables across the three D9THC treatment groups; and (2) would administering the high dose of D9THC in the same way as in the later part of the Laszlo study counteract a lack of patient compliance with increasing dose?
- (M) The applicant is frequently careless in the explanation of his statistical analyses. In Volume 1.1, pages 184 and 186, it is not clear whether we are dealing with the same patients but with "overall preference", for instance measured redundantly from two different patient record forms, or whether some special patient selection has taken place. The applicant has not provided an adequate explanation, or comparison. The same problem arises on pages 204 and 206. Another example comes from the Chang study. Comparing pages 506 and 515 in Volume 1.2, it is not clear what treatment group is under analysis on page 505 and which of the THC-placebo cycles is being analysed.
- (N) In the Frytak study, the applicant failed to analyze the global evaluation scale at days 2, 3, and 4 when a weaker emetic stimulus was used (Vol. 1.1, page 387). First this reviewer finds that the applicant's analysis exaggerates the significance level of the D9THC-placebo comparison at day 1 (p=.12 rather than p=.05). Next an analysis by this reviewer of days 2, 3, and 4 using the Wilcoxon rank sum test showed that only at day 3 was D9THC statistically superior to placebo. These results agree with the applicant's findings for day 1, 2, 3, and 4 using the Nausea and Vomiting scale (Vol. 1.1, page 386). The applicant did not compare Compazine to placebo statistically on the global evaluation scale. This reviewer found that only on day 3 was Compazine superior to placebo which was incidentally the only day that D9THC was found superior to placebo.

(0) In the Ungerleider study, the applicant has not indicated (Vol. 1.1, page 186) to which patient-data combination these data are to apply. In a conversation with Dr. McBride, Unimed statistical consultant, it was learned that the analysis on page 184 related to FORM-B and the analysis on page 186 related to FORM-C of the Ungerleider protocol (Vol. 1.8, pages 2376-2391).

5. Comments which may be conveyed to the Applicant

This submission contains only weak statistical evidence to support the applicant's labeling claim, that delta-9-tetrahydrocannabinol is effective in the prevention of nausea and vomiting induced by certain toxic anticancer agents.

(1) In none of the eight studies contained in this submission can the statistical analyses be considered open to valid, unambiguous interpretation. This is primarily because the applicant has not, but should have, statistically analyzed (1) differences in demographic variables across sequence groups in the crossover studies of Chang, Klutin-Nelians, Schein, and Ungerleider and across treatment groups in the studies of Frytak and Levitt, and (2) strength of emetic stimulus in the studies of Levitt, Schein, and Ungerleider. The purpose of such analysis is to investigate whether the statistical treatment comparisons in the present submission could or could not have been obscured both in crossover and parallel group studies by differences in patient groups resulting from an unfortunate randomization.

(ii) In the studies of Laszlo and Ekert, the control drugs were those anti-emetic therapies to which the patient historically had not responded. The design of these studies was such that statistical results can not be reliably extrapolated to those obtainable from a double-blind, randomized, controlled clinical trial.

(iii) The present submission lacks intermediate tables which permit the statistical reviewer to evaluate independently the applicant's statistical results. A useful pair of tables which is found in none of the crossover studies would be a display for each sequence group of the number of patients who received severity of nausea score i for D9THC and severity of nausea score j for control drug. Even in the parallel group study of Levitt, one can not find such a compact, elementary table as the number of patients having specified nausea scores using D9THC and using control drug.

(iv) In the studies of Ungerleider, Frytak and Chang, the applicant provided statistical analyses of a fragment of the full global evaluation. In the Ungerleider study, he chose to compare D9THC to Compazine only in patients who met the criteria for a "poor" responder (Vol. 1.1, page 182). In the Frytak study he compared D9THC to Compazine in "complete" responders (Vol. 1.2, page 387). In the Chang

- study (Vol. 1.2, page 509) he compared D9THC to placebo in patients receiving a rating of "excellent" or "partial." The applicant should analyse the full spectrum of response as a basis for comparing treatments.
- (v) In the studies of Schein and Ekert, the logical definitional structure of the global evaluation scale is such that certain patients can be simultaneously classified into two different categories. This is either a technical error or an incorrectly stated definition. For instance, in the Ekert study, a patient who is found to have Grade II nausea and Grade I vomiting simultaneously meets the criteria for having a complete response and the criteria for having a partial response (Vol. 1.2, page 403). In the Schein study, a patient having severe nausea and moderate vomiting is both a partial responder and a poor responder (Vol. 1.1, pages 273-274). The applicant needs to identify if a double standard of classification was followed.
- (vi) In the Ungerleider study, the results of the parametric analyses of variance of the crossover model are in question. In addition to comment (i) above, the data themselves appear to be severely non-normal (Vol. 1.1, pages 180 and 200). The applicant needs to define clearly how the study variable MD was calculated both for complete and for missing data and either show that the distribution of this variable meets the parametric analysis assumptions or perform an appropriate nonparametric analysis.
- (vii) In the Ungerleider study, the analysis of the patient's global evaluation can not be interpreted. This is because, in addition to comment (iv), the applicant attempted without justification to compare D9THC to Compazine in analyses (Vol. 1.1, pages 182 and 184) which involved period 2 based data despite the fact that in the analysis on page 178, Volume 1.1, it was shown that a statistically significant sequence effect was found to be present.
- (viii) The applicant has not supplied the appropriate randomization schedule for each of the eight studies in this submission.
- (ix) In numerous statistical analyses, a sequence effect was ignored without any attempt to justify this omission. The applicant should consider sequence effects in the statistical analyses given in Volumes 1.1 and 1.2 on pages 182, 184, 186, 204, 206, 295, 297, 298, and 509.
- (x) The Levitt study is negative on statistical grounds. Not only did this relatively large study not show a statistical dose-response relationship in the efficacy variables, but no statistical differences were found for these efficacy variables between D9THC, the positive control drug, and placebo. In some cases this may be due to the use of 7 point hedonic scales (Vol. 1.1, page 313, 316) which were given verbal anchor points only at both extremes of the scale. The fact

that the scales were verbally undefined on the 5 remaining middle values made it difficult for the investigator to use these scores consistently between the first and last patient entering the study and this consequently interferes with the interpretation of the statistical analysis of such a scale.

(xi) In the Frytak study, the applicant analyzed the nausea and vomiting scale at each of the four evaluation days. However, without explanation, he analyzed the global evaluation scale at day 1 only (Vol. 1.2, page 387) using a statistical method which treated a 3 level response scale as if there were only 2 levels (see comment (iv)). The result of this procedure was to show D9THC superior to placebo at the 5% significance level when in fact the per-comparison significance level is about 12% when the statistical reviewer took all 3 categories of response into account.

(xii) In the Chang study, Table 9. (Volume 1.2, page 506) the applicant did not indicate to which patients the analysis was applicable. It is assumed that these were patients receiving Methotrexate. The applicant has attempted to combine Methotrexate and Adriamycin/Cytosin treated patients in his statistical analyses on pages 508, 509, and 515. He should justify why such a combination should be considered valid for the interpretation he has in mind.

(xiii) In the study of Kluin-Nelmanns, the applicant stated that data from the first treatment period only were analyzed. In each period, there were eight days of treatment and according to patient record forms (Vol. 1.11, pages 4010-4064), there were 4 evaluations. The applicant did not indicate, in his statistical analyses, how sums of scores are appropriate when some of the four evaluations are missing.

(xiv) In the section giving the applicant's statistical considerations and conclusions in Volume 1.2, pages 576-588, the applicant gives numerous statistics in the form t=one number/another number with no explanation of how or where the numbers going into these ratios were obtained. It is impossible to evaluate the validity of any of these statistics.

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Mathematical Statistician

cc: Orig. NDA 18-651
HFD-120 HFD-150/Dr. Johnson
HFD-180/Dr. Lissok HFD-232/Dr. Dubey
HFD-232/Dr. Stein Chron
File: DRU 1.32 NDA
RAStein/pak/rb/9-21-81/#57478
Concur: Dr. Senturia 12/21/81
Dr. Dubey 10/11/81

APPENDIX

TABLE 1: Study Characteristics

TABLE 2: Study Variable by Investigator

TABLE 1

(1)	(2)	(3)	(4)	(5)	(4)
# Patients	Design	Blinding	Control	Randomized	THC Dose (mg/m ²)
					Pretreatment Measure of Eff. VARS.

Chang	24	X	Sgle	-	Y	10	?
Ekert	18	0	0	0	N	10	Y
Flytak	116	//	DB1	+-	Y	15*	N
Kluin-N.	3	X	DB1	-	Y	10	Y
Laszlo	108	0	0	0	N	5-15	Y
Levitt	117	//	DB1	+-	Y	5-15*	N
Schein	32	X	DB1	+	Y	15	N
Ungerleider	97	X	DB1	+	Y	7.5-12.5	Y

- (1) X signifies crossover of treatments
- // signifies parallel groups of treatments
- (2) 0 signifies unblinded
- Sgle signifies single-blind
- DB1 signifies double-blind
- (3) 0 signifies uncontrolled
- signifies negative control (Pbo)
- + signifies positive control(s)
- (4) Y signifies yes
- N signifies no
- * signifies dose in mg

TABLE 2

Investigator	Study Variable (Efficacy)
ALL	Investigator's Global Evaluation
2	Patient's Global Evaluation (2 scales)
3	Patient's Drug Preference
4	C, E, K, Lz, Lv, S
5	E, K, Lz, Lv, S
6	F, U
7	C, Lz, S
8	Lz, S
9	Lv
10	Lv
11	C
12	C
13	F, Lv
14	F
15	Lv
16	S
17	F
	# of patients dropping out for all reasons
	# of patients dropping out at crossover to second drug
	# of patients dropping out at second chemotherapy course
	# of patients dropping out due to side effects
	# of patients dropping out due to lack of efficacy
	Total # of Vomiting and Retching episodes
	Total volume of emesis
	Time to onset of Vomiting
	Time to onset of Nausea
	Duration of Vomiting
	Duration of Nausea
	Combined Nausea and Vomiting severity scale
	Vomiting severity scale
	Nausea severity scale
	Patient's Drug Preference
	Patient's Global Evaluation (2 scales)

C = Chang
 E = Ekerit
 F = Frytak
 K = Kluin-Nelmanns
 Lz = Lazzio
 Lv = Levitt
 S = Schein
 U = Ungelieder