

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION: NDA 18651/S011**

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Correspondence			X	

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: NDA 18651/S011**

**Trade Name: Marinol 2.5 mg, 5 mg, and 10 mg Capsules**

**Generic Name: (dronabinol)**

**Sponsor: Unimed Pharmaceuticals, Inc.**

**Approval Date: August 5, 1999**

**Indication: Provides for changes to the physician package insert and patient information insert per Unimed's petition to reschedule Marinol from CII to CIII according to the Drug Enforcement Administration (DEA)**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: NDA 18651/S011**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 18-651/S-011

AUG 05 1999

Unimed Pharmaceuticals, Inc.  
2150 E. Lake Cook Road  
Suite 210  
Buffalo Grove, Illinois 60089

Attention: Donald R. Peckels  
Director, Regulatory Affairs

Dear Mr. Peckels:

Please refer to your supplemental New Drug Application dated June 24, 1999, received June 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marinol (dronabinol) 2.5 mg, 5 mg, and 10 mg capsules.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental New Drug Application provides for changes to the physician package insert and patient information insert per Unimed's petition to reschedule Marinol from CII to CIII according to the Drug Enforcement Administration (DEA) notification in the Federal Register Notice of July 2, 1999, to transfer from schedule II to schedule III of the Controlled Substance Act (CSA) of the drug containing synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules (Marinol). Your submission stated July 24, 1999 as the implementation date for the changes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted June 24, 1999, patient package insert submitted June 24, 1999) with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

It is recommended that at the beginning of the labeling, the paragraph that currently reads:

Should be changed to read as follows:

It is further recommended that the section

be changed to:

STORAGE CONDITIONS

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-651/S-011." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

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

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

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

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

If you have any questions, contact Indira Kumar, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

/S/

Cynthia G. McCormick, M.D.

Director

Division of Anesthetic, Critical Care,  
and Addiction Drug Products, HFD-170

Office of Drug Evaluation II

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 18651/S011**

**FINAL PRINTED LABELING**

Labeling: Div 5

NDA No. 18-651

Rcd. 06-26-00

Reviewed by: \_\_\_\_\_

ROXANE LABORATORIES, INC.

## PATIENT INFORMATION

**MARINOL®** (Dronabinol) for use in the loss of appetite associated with weight loss in patients with AIDS.

### IMPORTANT

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. If a child puts a capsule in his or her mouth or swallows Marinol, take the medicine away from the child and contact a poison control center immediately, or contact a doctor immediately.

Do not drive a car or operate machinery until you know how Marinol affects you. While taking Marinol, do not drink alcohol, smoke marijuana, or take other drugs that have an effect on the central nervous system (such as sedatives or hypnotics). Unless advised by your doctor, do not use Marinol if you are pregnant or nursing.

### INTRODUCTION

This leaflet provides a summary of information about Marinol. Please read it and keep it with your medicines in case you need to look at it again. Ask your doctor, nurse, or pharmacist if you have any questions.

Marinol contains dronabinol (THC), which occurs naturally, and has been extracted from *Cannabis sativa* L. (marijuana).

### PRECAUTIONS

Be sure to tell your doctor if you have had any of the following:

- heart disease
- current or past drug abuse
- current or past alcohol abuse
- mental health problems (mania, depression, schizophrenia)
- allergies to drugs

If you become pregnant while taking Marinol, stop using it until you have talked to your doctor.

Marinol can dangerously interact with alcohol and with other drugs that have an effect on the central nervous system (such as Valium, Librium, Xanax, Seconal, Nembutal, or Phenobarbital).

Do not drive or operate machinery until you are sure how Marinol affects you and you are able to perform safely.

You may experience changes in mood or have other effects when first taking Marinol. Be sure that there is a responsi-

ble person nearby when you first take Marinol or when there is an adjustment in your dose.

Tell your doctor if you are taking any other prescription or nonprescription medicines.

Do not smoke marijuana while using Marinol. This can cause an overdose.

### INFORMATION ABOUT USING MARINOL

#### Introduction

Eating a nutritionally balanced diet is fundamental for all stages of life. For persons living with Human Immunodeficiency Virus (HIV), it's especially important to ensure an adequate diet to maintain an ideal weight and good nutritional status. There is some indication that optimal nutrition can help maintain the integrity of the immune system, and an adequate diet will allow you to better withstand the diseases associated with an AIDS diagnosis.

Many conditions, frequently interrelated, may cause a loss of appetite. Chewing and swallowing may become difficult or painful, due to inflammation or sores in your mouth and throat.

You may experience intermittent diarrhea or overall physical discomfort associated with AIDS. Sometimes, shopping for food and preparing adequate meals may drain your energy and desire to eat. Mental depression also may result in a loss of your appetite, or you simply may grow increasingly frustrated with repeated eating problems.

A loss of appetite may occur at various times during illness associated with HIV infection. It often leads to the selection of an inadequate diet. Because a poor nutrient intake can result in weight loss and malnutrition, it's important to learn to recognize and handle a temporary loss of your appetite.

Your doctor may prescribe an appetite stimulant such as Marinol. Marinol should be taken exactly as directed by your doctor, and indicated on the prescription label. You will most likely start therapy by taking one white capsule (2.5 mg) of Marinol twice daily, before lunch and supper. Your doctor may adjust your Marinol dosage if needed to maximize its effect or to de-

crease any side effects.

If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double your dose. Marinol must be swallowed whole to work effectively. Do not crush or chew the capsules.

It is important not to take sedatives, hypnotics, other mind altering substances, or alcohol, while taking Marinol without notifying your health care givers (physician, pharmacists and nurses). Do not drive or attempt other activities requiring full alertness while taking Marinol. Your doctor will advise when you may resume these activities.

Your doctor and pharmacist should be made aware of any other prescription medications or over-the-counter products you may be taking, as they could affect the way you respond to Marinol.

Remember to keep this and all other medication out of the reach of children.

Increasing your appetite is only the first step in improving your nutritional status. How, what and when you eat are also very important.

#### How to eat

The purpose of consuming an adequate diet, even at times when you don't feel like eating, is to maintain an ideal weight and good nutritional status. Key to an adequate diet for HIV-infected individuals are foods dense in calories and nutrients. In other words, when you find it difficult to eat, make the most of what you do consume by selecting foods that provide many calories or nutrients in each mouthful.

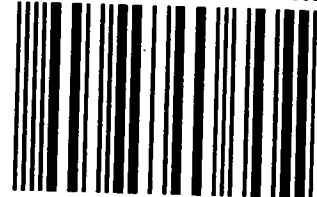
Try some of the following ideas to boost your food intake. Keep in mind the foods you previously may have limited in your diet, especially those higher in fat, now can provide a significant source of calories. Enjoy an ice cream sundae frequently!

Cool or cold foods can dull pain from mouth and throat sores; popsicles may even numb your mouth prior to eating a larger meal. The cooler temperatures also diminish the aroma of unappetizing food.

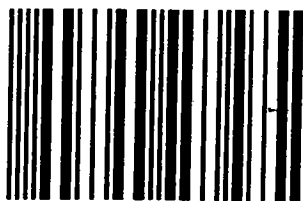
Blend one cup of nonfat dry milk pow-

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MARINOL®  
CAPSULES 



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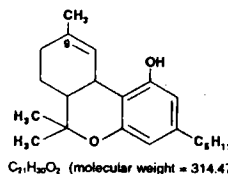
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ROXANE LABORATORIES, INC.

MARINOL®   
(dronabinol)  
Capsules

R<sub>x</sub> only.

Dronabinol is a cannabinoid designated chemically as (6a*R*-*trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-benzol[b,d]pyran-1-ol. Dronabinol has the following empirical and structural formulas:



Dronabinol, delta-9-tetrahydrocannabinol (delta-9-THC), is naturally-occurring and has been extracted from *Cannabis sativa* L. (marijuana).

Dronabinol is also chemically synthesized and is a light-yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pK<sub>a</sub> of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

Capsules for oral administration: Marinol is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each Marinol capsule is formulated with the following inactive ingredients: FD&C Blue No. 1 (5 mg), FD&C Red No. 40 (5 mg), FD&C Yellow No. 6 (5 mg and 10 mg), gelatin, glycerin, methylparaben, propylparaben, sesame oil, and titanium dioxide.

#### CLINICAL PHARMACOLOGY

Dronabinol is an orally active cannabinoid which, like other cannabinoids, has complex effects on the central nervous system (CNS), including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol and other cannabinoids.

**Pharmacodynamics:** Dronabinol-induced sympathomimetic activity may result in tachycardia and/or conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing.

Dronabinol also demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability.

After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacologic effects of dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol, administered orally in divided doses, for 16 days. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A decrease in supine blood pressure, made worse by standing, was also observed initially. These volunteers developed tolerance to the cardiovascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation.

Tachyphylaxis and tolerance do not, however, appear to develop to the appetite stimulant effect of Marinol. In studies involving patients with Acquired Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of Marinol has been sustained for up to five months in clinical trials, at dosages ranging from 2.5 mg/day to 20 mg/day.

#### Pharmacokinetics:

**Absorption and Distribution:** Marinol (dronabinol) is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic me-

vascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation.

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#### Pharmacokinetics:

**Absorption and Distribution:** Marinol (dronabinol) is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation. Dronabinol has a large apparent volume of distribution, approximately 10 L/kg, because of its lipid solubility. The plasma protein binding of dronabinol and its metabolites is approximately 97%.

The elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

**Metabolism:** Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 2 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution.

**Elimination:** Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radiolabeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces.

Following single dose administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

In a study of Marinol involving AIDS patients, urinary cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week period. The urinary cannabinoid/creatinine ratio was closely correlated with dose. No increase in the cannabinoid/creatinine ratio was observed after the first two weeks of treatment, indicating that steady-state cannabinoid levels had been reached. This conclusion is consistent with predictions based on the observed terminal half-life of dronabinol.

**Special Populations:** The pharmacokinetic profile of Marinol has not been investigated in either pediatric or geriatric patients.

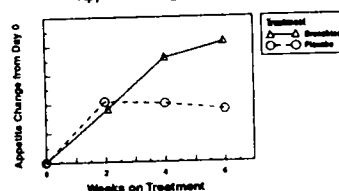
#### CLINICAL TRIALS

**Appetite Stimulation:** The appetite stimulant effect of Marinol (dronabinol) in the treatment of AIDS-related anorexia associated with weight loss was studied in a randomized, double-blind, placebo-controlled study involving 139 patients. The initial dosage of Marinol in all patients was 5 mg/day, administered in doses of 2.5 mg one hour before lunch and one hour before supper. In pilot studies, early morning administration of Marinol appeared to have been associated with an increased frequency of adverse experiences, as compared to dosing later in the day. The effect of Marinol on appetite, weight, mood, and nausea was measured at scheduled intervals during the six-week treatment period. Side effects (feeling high, dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper or bedtime.

As compared to placebo, Marinol treatment resulted in a statistically significant improvement in appetite as measured by visual analog scale (see figure). Trends toward improved body weight and mood, and decreases in nausea were also seen.

After completing the 6-week study, patients were allowed to continue treatment with Marinol in an open-label study, in which there was a sustained improvement in appetite.

Appetite Change from Baseline



**Antiemetic:** Marinol (dronabinol) treatment of chemotherapy-induced emesis was evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of various malignancies. The antiemetic efficacy of Marinol was greatest in patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's lymphomas. Marinol dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). As indicated in the following table, escalating the Marinol dose above 7 mg/m<sup>2</sup> increased the frequency of adverse experiences, with no additional antiemetic benefit.

Marinol Dose: Response Frequency and Adverse Experiences\*  
(N = 750 treatment courses)

Marinol Dose	Response Frequency (%)			Adverse Events Frequency (%)		
	Complete	Partial	Poor	None	Nondysphoric	Dysphoric
< 7 mg/m <sup>2</sup>	36	32	32	23	65	12
> 7 mg/m <sup>2</sup>	33	31	36	13	58	28

\* Nondysphoric events consisted of drowsiness, tachycardia, etc.

Combination antiemetic therapy with Marinol and a phenothiazine (prochlorperazine) may result in synergistic or additive antiemetic effects and attenuate the toxicities associated with each of the agents.

#### INDIVIDUALIZATION OF DOSAGES

The pharmacologic effects of Marinol (dronabinol) are dose-related and subject to considerable interpatient variability. Therefore, dosage individualization is critical in obtaining the maximum benefit of Marinol treatment.

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#### INDIVIDUALIZATION OF DOSAGES

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**Appetite Stimulation:** In the clinical trials, the majority of patients were treated with 5 mg/day Marinol, although the dosages ranged from 2.5 to 20 mg/day. For an adult:

1. Begin with 2.5 mg before lunch and 2.5 mg before supper.  
If CNS symptoms (feeling high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days with continued dosage.
2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If symptoms continue to be a problem, taking the single dose in the evening or at bedtime may reduce their severity.
3. When adverse effects are absent or minimal and further therapeutic effect is desired, increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies.

The pharmacologic effects of Marinol are reversible upon treatment cessation.

**Antiemetic:** Most patients respond to 5 mg three or four times daily. Dosage may be escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results. Therapy should be initiated at the lowest recommended dosage and titrated to clinical response. Administration of Marinol with phenothiazines, such as prochlorperazine, has resulted in improved efficacy as compared to either drug alone, without additional toxicity.

**Pediatrics:** Marinol is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing Marinol for children because of the psychoactive effects.

**Geriatrics:** Caution is advised in prescribing Marinol in elderly patients because they are generally more sensitive to the psychoactive effects of drugs. In antiemetic studies, no difference in tolerance or efficacy was apparent in patients > 55 years old.

#### INDICATIONS AND USAGE

Marinol (dronabinol) is indicated for the treatment of:

1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

#### CONTRAINDICATIONS

Marinol (dronabinol) is contraindicated in any patient who has a history of hypersensitivity to any cannabinoid or sesame oil.

#### WARNINGS

Patients receiving treatment with Marinol should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

#### PRECAUTIONS

**General:** The risk/benefit ratio of Marinol (dronabinol) use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects of Marinol.

Marinol should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia (see CLINICAL PHARMACOLOGY).

Marinol should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse Marinol as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance.

Marinol should be used with caution and careful psychiatric monitoring in patients with mania, depression, or schizophrenia because Marinol may exacerbate these illnesses.

Marinol should be used with caution in patients receiving

concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

Marinol should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these patient populations.

Marinol should be used with caution for treatment of anorexia and weight loss in elderly patients with AIDS because they may be more sensitive to the psychoactive effects and because its use in these patients has not been studied.

**Information for Patients:** Patients receiving treatment with Marinol (dronabinol) should be alerted to the potential for additive central nervous system depression if Marinol is used concomitantly with alcohol or other CNS depressants such as benzodiazepines and barbiturates.

Patients receiving treatment with Marinol should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

Patients using Marinol should be advised 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 the supervision of a responsible adult during initial use of Marinol and following dosage adjustments.

**Drug Interactions:** In studies involving patients with AIDS and/or cancer, Marinol (dronabinol) has been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions. Although no drug/drug interactions were discovered during the clinical trials of Marinol, cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering dronabinol to patients receiving other highly protein-bound drugs. Published reports of drug/drug interactions involving cannabinoids are summarized in the following table.

CONCOMITANT DRUG	CLINICAL EFFECT(S)
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive or super-additive tachycardia, drowsiness
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness
Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, other CNS depressants	Additive drowsiness and CNS depression
Disulfiram	A reversible hypomanic reaction was reported in a 28 y/o man who smoked marijuana; confirmed by dechallenge and rechallenge
Fluoxetine	A 21 y/o female with depression and bulimia receiving 20 mg/day fluoxetine X 4 wks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Artipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism
Theophylline	Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies have not been performed with dronabinol. Mutagenicity testing of dronabinol was negative in an Ames test. In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30 to 150 mg/m<sup>2</sup>, equivalent to 0.3 to 1.5 times maximum recommended human dose (MRHD) of 90 mg/m<sup>2</sup>/day in cancer patients or 2 to 10 times MRHD of 15 mg/m<sup>2</sup>/day in AIDS patients, 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.

**Pregnancy:** Pregnancy Category C. Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m<sup>2</sup>, equivalent to 0.2 to 5 times maximum recommended human dose (MRHD) of 90 mg/m<sup>2</sup>/day in cancer patients or 1 to 30 times MRHD of 15 mg/m<sup>2</sup>/day in AIDS patients, and in rats at 74 to 295 mg/m<sup>2</sup> (equivalent to 0.8 to 3 times MRHD of 90 mg/m<sup>2</sup> in cancer patients or 5 to 20 times MRHD of 15 mg/m<sup>2</sup>/day in AIDS patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Dronabinol should be used only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** Use of Marinol is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

#### ADVERSE REACTIONS

Adverse experiences information summarized in the tables below was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to Marinol (dronabinol). Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days. Studies of nausea and vomiting related to cancer chemotherapy included 217 patients receiving dronabinol and 68

can transmit hepatitis virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

#### ADVERSE REACTIONS

Adverse experiences information summarized in the tables below was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to Marinol (dronabinol). Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) has been reported by patients receiving Marinol in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%) (see CLINICAL TRIALS).

The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving Marinol. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter.

**PROBABLY CAUSALLY RELATED:** Incidence greater than 1%.

Rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317). Rates were generally higher in the anti-emetic use (given in parentheses).

*Body as a whole:* Asthenia.

*Cardiovascular:* Palpitations, tachycardia, vasodilation/facial flush.

*Digestive:* Abdominal pain\*, nausea\*, vomiting\*.

*Nervous system:* (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness\*, euphoria\*, (hallucination), paranoid reaction\*, somnolence\*, thinking abnormal\*.

\* Incidence of events 3% to 10%.

**PROBABLY CAUSALLY RELATED:** Incidence less than 1%.

Event rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317).

*Cardiovascular:* Conjunctivitis\*, hypotension\*.

*Digestive:* Diarrhea\*, fecal incontinence.

*Musculoskeletal:* Myalgias.

*Nervous system:* Depression, nightmares, speech difficulties, tinnitus.

*Skin and Appendages:* Flushing\*.

*Special senses:* Vision difficulties.

\* Incidence of events 0.5% to 1%.

**CAUSAL RELATIONSHIP UNKNOWN:** Incidence less than 1%.

The clinical significance of the association of these events with Marinol treatment is unknown, but they are reported as alerting information for the clinician.

*Body as a whole:* Chills, headache, malaise.

*Digestive:* Anorexia, hepatic enzyme elevation.

*Respiratory:* Cough, rhinitis, sinusitis.

*Skin and Appendages:* Sweating.

#### DRUG ABUSE AND DEPENDENCE

Marinol (dronabinol) is one of the psychoactive compounds present in cannabis, and is abusable and controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.

Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgement, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of Marinol for therapeutic purposes.

In an open-label study in patients with AIDS who received Marinol for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse.

An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs and anorexia.

These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperarousal) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol.

#### OVERDOSAGE

Signs and symptoms following MILD Marinol (dronabinol) intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/70kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of Marinol.

**Management:** A potentially serious oral ingestion, if

ceived Marinol for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse.

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These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol.

#### OVERDOSAGE

Signs and symptoms following MILD Marinol (dronabinol) intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/70kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of Marinol.

**Management:** A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam po) may be used for treatment of extreme agitation. Hypotension usually responds to Trendelenburg position and IV fluids. Pressors are rarely required.

#### DOSAGE AND ADMINISTRATION

**Appetite stimulation:** Initially, 2.5 mg Marinol (dronabinol) should be administered orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this 5 mg/day dosage of Marinol, the dosage can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. If clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day Marinol, administered in divided oral doses. Caution should be exercised in escalating the dosage of Marinol because of the increased frequency of dose-related adverse experiences at higher dosages (see PRECAUTIONS).

**Antiemetic:** Marinol is best administered at an initial dose of 5 mg/m<sup>2</sup>, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m<sup>2</sup> dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m<sup>2</sup> increments to a maximum of 15 mg/m<sup>2</sup> per dose. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose (see PRECAUTIONS).

#### SAFETY AND HANDLING

Marinol (dronabinol) should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F). Protect from freezing. No particular hazard to health care workers handling the capsules has been identified.

#### HOW SUPPLIED

**MARINOL® CAPSULES** (dronabinol solution in sesame oil in soft gelatin capsules)

2.5 mg white capsules (Identified RL).

NDC 0054-2601-11: Bottles of 25 capsules.

NDC 0054-2601-21: Bottles of 60 capsules.

NDC 0054-2601-25: Bottles of 100 capsules.

5 mg dark brown capsules (Identified RL).

NDC 0054-2602-11: Bottles of 25 capsules.

NDC 0054-2602-25: Bottles of 100 capsules.

10 mg orange capsules (Identified RL).

NDC 0054-2603-11: Bottles of 25 capsules.

NDC 0054-2603-21: Bottles of 60 capsules.

MARINOL® is a registered trademark of Unimed Pharmaceuticals, Inc. and is marketed by Roxane Laboratories, Inc. under license from Unimed Pharmaceuticals, Inc. Manufactured by Banner Pharmacaps, Inc. Chetworth, CA 91311

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Revised June 1999  
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 **Roxane**  
Laboratories, Inc.  
Columbus, Ohio 43216

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 18651/S011**

**ADMINISTRATIVE DOCUMENTS**

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

CONSUMER SAFETY OFFICER REVIEW

AUG 05 1999

**Application Number:** NDA 18-651/SLR 011

**Name of Drug:** Marinol (dronabinol) Capsules

**Sponsor:** Unimed Pharmaceuticals, Inc.

**RPM:** Indira Kumar

**Material Reviewed**

Final Printed Label (physician package insert) per Unimed's petition to reschedule Marinol from CII to CIII according to the Drug Enforcement Administration (DEA) notification in the Federal Register Notice of July 2, 1999, to transfer from schedule II to schedule III of the Controlled Substance Act (CSA) of the drug containing synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules (Marinol) approved by FDA, with the last approved physician package insert of June 17, 1993. Unimed Pharmaceuticals, Inc proposed patient Information leaflet was reviewed with the last approved patient package insert of June 17, 1993.

**Submission Date:** June 24, 1999

**Receipt Date:** June 25, 1999

**Background and Summary Description:**

In accordance with 21 CFR 314.70(c), Unimed Pharmaceuticals, Inc. has submitted a labeling supplement for NDA 18-651 for Marinol (dronabinol) capsules to provide for revised, final-printed labeling (physician package insert and patient information leaflet).

**Status Report**

**Reviews Completed:**

Control Substance Evaluation Team (CSET)/ Chemistry: Silvia Calderon, Ph.D., Michael Klein, Ph.D., Albinus D'Sa, Ph.D. - 8-3-99

CSO Review: Indira Kumar - 8-4-99

**Reviews Pending:** None



**CSO Review**

Please note that the sponsor's proposed revisions are indicated by strikeovers and underlined text.

**PHYSICIAN PACKAGE INSERT**

**BOX WARNING:** Not Applicable

**DESCRIPTION:**

Heading:

Line 2 - changed to \_\_\_\_\_

Line 5 - Rx only was added.

Line 6 - was deleted.

Paragraph 4:

Line 4,5,6 - FD&C Blue No. 1 (5 mg), FD&C Red No. 40 (5 mg), FD&C Yellow No. 6 (5 mg and 10 mg) was added.

**CLINICAL PHARMACOLOGY:** No changes noted.

**INDICATIONS AND USAGE:** No changes noted.

**CONTRAINDICATIONS:** No changes noted.

**WARNINGS:**

Paragraph 1: As follows was deleted.

**PRECAUTIONS:** No changes noted.

**ADVERSE REACTIONS:** No changes noted.

**DRUG ABUSE AND DEPENDENCE:**

Paragraph 1:

Line 3 - was changed to

**OVERDOSAGE:** No changes noted.

**DOSAGE AND ADMINISTRATION:** No changes noted.

**SAFETY AND HANDLING:**

Paragraph 2: Was deleted.

**HOW SUPPLIED:**

New line 3 under heading: **2.5 mg white capsules (Identified RL).**

Added - NDC 0054-2601-25: Bottles of 100 capsules.

New line 2 under heading: **5 mg dark brown capsules (Identified RL).**

Added - NDC 0054-2602-25: Bottles of 100 capsules.

New line 2 under heading: **10 mg orange capsules (Identified RL).**

Added - NDC 0054-2603-21: Bottles of 60 capsules.

Last Lines: Were deleted.

**PATIENT INFORMATION**

Heading:

changed to

**IMPORTANT:** Line 6 – was changed to

**INTRODUCTION:** No changes noted.

**PRECAUTIONS:** No changes noted.

**INFORMATION ABOUT USING MARINOL:**

**Introduction:**

Paragraph 9: Was deleted

**How to eat:** No changes noted.

**What to eat:** No changes noted.

**When to eat:** No changes noted.

**Storage Instructions:** No changes noted.

**If You Are Taking Medicines:** No changes noted.

**What to Watch For (Adverse Effects):** No changes noted.

**If You Have Problems in the First Few Days:** No changes noted.

Last Line: changed to

With the changes noted above, I recommend approval of this labeling supplement.

IS/ 8/5/99  
Regulatory Project Manager – Indira Kumar

IS/ 8-5-99  
Supervisory Comment/Concurrence – Corinne P. Moody

**Review Concurrence:**

**Abuse Liability:** Silvia Calderon, Ph.D. IS/

**Chemistry:** Albinus D'Sa, Ph.D. IS/

**Medical:** Chang Q. Lee, M.D. IS/

Celia Winchell, M.D. IS/

**Division Director:** Cynthia G. McCormick, M.D. IS/

AUG 05 1999

NDA# 18651, SLR-011

**SUPPLEMENT CLAIMS FOR:** Changes made in response to the rescheduling of Marinol® from Schedule II to Schedule III of the Controlled substances Act.

**PROPOSED CHANGES:**

1. Controlled Substances symbol was changed to in the following sections:
  - a. The beginning of the labeling.
  - b. **DRUG ABUSE AND DEPENDENCE** (First paragraph). In addition, reference to was changed to

**RECOMMENDATION:** Change ACCEPTED. Final Rule on the Rescheduling of Marinol® has been issued on July 2, 1999, and published in the Federal Register, Vol. 64, No. 127, 35928-35930.
2. The first paragraph under **WARNINGS** was deleted. This paragraph was worded as follows:

**RECOMMENDATION:** Change ACCEPTED. Schedule II controls no longer apply to Marinol. In addition there is no substantial evidence of diversion of Marinol.

3. The second paragraph under **SAFETY AND HANDLING** was deleted. This paragraph was formerly reading:

**RECOMMENDATION:** Change ACCEPTED. It is also recommended to change the title of this section from to  
Also it is recommended to remove the sentence currently at the end of this section.  
The section that reads as follows:

Should read as:

4. The statement, \_\_\_\_\_ was deleted from the HOW SUPPLIED section.  
**RECOMMENDATION:** Change ACCEPTED. DEA order form is not required for Schedule III drugs.
5. The color additives FD&C Blue No. 1 and FD&C Red No. 40 were added to the list of inactive ingredients.  
**RECOMMENDATION:** Change ACCEPTED
6. Replacement of the statement \_\_\_\_\_ by \_\_\_\_\_ is proposed  
**RECOMMENDATION:** Change ACCEPTED, based on the provision set by FDA Modernization Act of 1997, Sect. 126:
7. Deletion of the statement, \_\_\_\_\_ proposed  
**RECOMMENDATION:** Change ACCEPTED, according to CFR 369.22

#### PATIENT INFORMATION LEAFLET CHANGES

1. Controlled Substances symbol \_\_\_\_\_ was changed to \_\_\_\_\_ at the beginning of the labeling
2. The ninth paragraph under the section \_\_\_\_\_ that read "  
\_\_\_\_\_  
\_\_\_\_\_ was deleted.
3. Grammatical correction in the second paragraph under IMPORTANT

**RECOMMENDATION:** Changes accepted based on the current CIII status of the drug product.

## CONCLUSIONS AND RECOMMENDATION

Most of the changes proposed by the Sponsor are accepted. It is recommended that the title of section be changed to

As per 21 CFR 201.57 (k) (4) this section could be included under the HOW SUPPLIED header. Also in the same section it is recommended to delete the sentence that currently is at the end of the section and incorporate that the product could be alternatively stored in a refrigerator, as per USP-NF, Tenth Supplement, page 4765. The section should read:

It is also recommended that at the beginning of the labeling, the paragraph that currently read:

Be changed to read as:

Reviewer:

/S/

Silvia N. Calderon, Ph.D.  
Interdisciplinary Scientist

8-5-99

Date

Concur

Michael Klein, Ph.D.  
Team Leader, Controlled  
Substances Evaluation Team

Date

Concur

/S/

Albinus D'Sa, Ph.D.  
Chemist Team Leader

8/5/99

Date

Concur

/S/

Cynthia G. McCormick, M.D.  
Division Director,  
Division of Anesthetic, Critical  
Care and Addiction Drug Products, HFD-170

8-5-99

Date