PRODUCT MONOGRAPH

^{N}MARINOL®

dronabinol (delta-9-tetrahydrocannabinol; Δ^9-THC)

2.5 mg, 5 mg, and 10 mg capsules

Antiemetic

DATE OF PREPARATION:
December 3, 2002

DATE OF REVISION:
May 4, 2007

SOLVAY PHARMA
60 Columbia Way, Suite 102, Markham, Ontario L3R 0C9

Control No.: 112007

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY OF PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 5
DRUG ABUSE AND DEPENDENCE 6
ADVERSE REACTIONS 8
DRUG INTERACTIONS 10
DOSAGE AND ADMINISTRATION 11
OVERDOSAGE 13
ACTION AND CLINICAL PHARMACOLOGY 14
STORAGE AND STABILITY 17
DOSAGE FORMS, COMPOSITION AND PACKAGING 17
PART II: SCIENTIFIC INFORMATION 18
PHARMACEUTICAL INFORMATION 18
CLINICAL TRIALS 19
DETAILED PHARMACOLOGY 20
PART III: CONSUMER INFORMATION 29

[N]MARINOL®

dronabinol (delta-9-tetrahydrocannabinol; Δ^9-THC)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	2.5 mg capsule	Sesame oil
	5 mg capsule	Iron oxide red, iron oxide black, sesame oil
	10 mg capsule	Iron oxide red, iron oxide yellow, sesame oil

For a complete list of non-medicinal ingredients see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Adults:

MARINOL (dronabinol) may be of value in the treatment of:

- AIDS-related anorexia associated with weight loss
- severe nausea and vomiting associated with cancer chemotherapy

MARINOL is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused. The active component THC is scheduled under the Controlled Drugs and Substances Act and as such cannot be used or prescribed except for its recognized indications.

Long-term use of MARINOL:

MARINOL has not been systematically evaluated beyond 6 weeks in controlled clinical trials for AIDS-related anorexia associated with weight loss. The physician who elects to use MARINOL for extended periods in this indication should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Geriatrics (>65 years of age):

Evidence from clinical studies and experience indicates that elderly patients are generally more sensitive to the psychoactive effects of drugs and a brief discussion can be found in the appropriate sections (WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; **DOSAGE AND ADMINISTRATION, Geriatrics).**

Pediatrics (<18 years of age):
The safety and efficacy of MARINOL have not been established in adolescents or children under 18 years of age, therefore MARINOL should not be used in adolescents or children (see **CONTRAINDICATIONS)**.

CONTRAINDICATIONS

MARINOL (dronabinol) is contraindicated in

- patients with known or suspected allergy to marijuana, other cannabinoids or sesame oil
- patients with significant hepatic or renal impairment
- patients with serious cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure
- patients with a history of schizophrenia or any other psychotic disorder
- children under 18 years of age
- women of child-bearing potential not on a reliable contraceptive or men intending to father a child (see "Use in Women of Child-Bearing Potential")
- pregnant or nursing women (see "Use in Women of Child-Bearing Potential")

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC, the active component of MARINOL, can produce physical and psychological dependence and has the potential for being abused.

THC has complex effects on the central nervous system, some of which are called "intoxication type reactions". These can result in changes of mood, decrease in cognitive performances and memory, decrease in ability to control drives and impulses, and alteration of the perception of reality, particularly altered time sense. Fainting episodes have been observed with use of cannabinoids. "Intoxication type reactions" (feeling drunk, disturbance in attention, dizziness, somnolence, disorientation, dissociation, euphoric mood, etc.) appear to be dose-related, increasing in frequency with higher dosages, and subject to great inter-patient variability. They usually remit on reduction of doses, increasing the interval between doses or interruption of the drug. Because of the potential of THC to alter the mental state, MARINOL should be used only as indicated and prescriptions should be limited to the amount necessary for the period between clinic visits.

Drug administration should be discontinued in patients experiencing a psychotic reaction and the patient should be closely observed in an appropriate setting until his/her mental state returns to normal. Patients should be warned not to drive or engage in activities requiring unimpaired judgement and coordination.

Cannabinoids have cardiovascular effects that include tachycardia, and transient changes in blood pressure, including episodes of postural hypotension. Use of MARINOL is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure.

Published reports on cannabinoids are equivocal with regard to the effects of THC on seizure threshold. Until further information is available, caution should be used when treating patients with a history of epilepsy or recurrent seizures.

General

The risk/benefit ratio of MARINOL use should be carefully evaluated because of individual variation in response and tolerance to the effects of MARINOL.

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis

see TOXICOLOGY for animal data.

Cardiovascular
MARINOL is not recommended in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia (see CONTRAINDICATIONS, and CLINICAL PHARMACOLOGY).

DRUG ABUSE AND DEPENDENCE
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 is one of the psychoactive compounds present in cannabis, and is abusable and controlled (Schedule II) under the Controlled Drugs and 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 (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.

Neurologic
Patients receiving treatment with MARINOL 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.

Psychiatric

MARINOL should not be used in patients with mania, depression, or schizophrenia because MARINOL may exacerbate these illnesses (see **CONTRAINDICATIONS**).

MARINOL should be used with caution, if at all, in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

Patients using MARINOL should be advised of possible changes in mood and other adverse behavioural 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.

Use in Women of Child-Bearing Potential

Independent research in laboratory species has found that cannabinoids have been associated with evidence of reproductive toxicity in early gestation and have been found to affect spermatogenesis. Therefore women of child-bearing potential should take reliable contraceptive precautions for the duration of treatment and for three months after discontinuation of therapy. Male patients with a partner of childbearing potential should ensure that reliable contraceptive precautions are maintained for the duration of therapy and for three months after discontinuation of therapy.

Special Populations

Pregnant Women: The safe use of MARINOL during pregnancy has not been established.

Reproduction studies with delta-9-tetrahydrocannabinol have been performed in mice at 15 to 450 mg/m^2 , equivalent to 0.2 to 5 times maximum recommended human dose (MRHD) of 90 mg/m^2 /day in cancer patients or 1 to 30 times MRHD of 15 mg/m^2 /day in AIDS patients, and in rats at 74 to 295 mg/m^2 (equivalent to 0.8 to 3 times MRHD of 90 mg/m^2 in cancer patients or 5 to 20 times MRHD of 15 mg/m^2 /day in AIDS patients). These studies have revealed no evidence of teratogenicity due to delta-9-tetrahydrocannabinol. At these dosages in mice and rats, delta-9-tetrahydrocannabinol 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. Animal studies have indicated that cannabinoids may have detrimental effects on foetal development. There are no adequate and well-controlled studies in pregnant women. MARINOL is contraindicated in pregnant women. MARINOL should not be used in women who intend to become pregnant.

Nursing Women: There is evidence that delta-9-tetrahydrocannabinol is concentrated

in and secreted in human breast 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 (see CONTRAINDICATIONS).

Pediatrics: Animal data have indicated that cannabinoids interfere with development of neonatal and adolescent rodents. MARINOL is contraindicated in children under 18 years of age.

Geriatrics: Clinical studies of MARINOL in AIDS and cancer patients did not include the sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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.

During controlled clinical trials, the most commonly encountered events in anti-emetic studies were drowsiness, dizziness and transient impairment of sensory and perceptual functions; and, in studies in AIDS patients, euphoria, dizziness, somnolence and thinking abnormalities.

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%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following tables list the adverse reactions experienced by 474 MARINOL-treated

patients participating in 11 controlled clinical trials. Studies of AIDS-related weight loss included 157 patients receiving MARINOL at 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. In AIDS patients treated up to 5 months, adverse events related to MARINOL were not related to duration of therapy. Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving MARINOL and 68 receiving placebo.

Frequency of Adverse Reactions From Clinical Trials in Chemotherapy - Related Nausea (N=317) and AIDS-Related Anorexia N=157)

A. Probably Causally Related: Incidence >1%

Body as a whole:	Asthenia
Nervous System:	amnesia**, anxiety/nervousness, ataxia**, confusion, depersonalization, dizziness*, euphoria*, hallucination**, paranoid reaction*, somnolence*, thinking abnormal*
Digestive:	abdominal pain*, nausea*, vomiting
Cardiovascular:	palpitation, tachycardia, vasodilation/facial flush

*incidence 3-10%
** rates generally higher in the antiemetic use

B. Probably Causally Related: Incidence <1%

Nervous System:	depression, nightmares, speech difficulties, tinnitus
Digestive:	diarrhea*, faecal incontinence
Cardiovascular:	hypotension*
Musculoskeletal:	Myalgias
Skin/Appendages:	flushing*
Special Senses:	vision difficulties, conjunctivitis*

*incidence 0.3-1%

C. Causal Relationship Unknown: Incidence <1%
The clinical significance of the association of these events with MARINOL® Capsules 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/Appendages:	Sweating

Post-Market Adverse Drug Reactions

In addition to those adverse events reported during clinical trials, the following side effects have been identified during post-marketing use of dronabinol. These reactions are reported voluntarily. It is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. A frequency of < 1% is assumed:

Immune system disorders:
Hypersensitivity reactions

Nervous system disorders:
Seizures and seizure like activity

Skin and subcutaneous tissue disorders:
Allergic skin reactions (e.g. rash, pruritus)

General disorders and administrative site reactions:
Fatigue, dry mouth, drug ineffective

Injury, poisoning and procedural complications:
Falls

DRUG INTERACTIONS

Serious Drug Interactions

- Care should be taken with sedatives, drugs with sedating effect and hypnotics as co-administration with MARINOL may have an additive effect.
- Alcohol may interact with MARINOL, particularly in affecting coordination, concentration and ability to respond quickly.

Overview

In studies involving patients with AIDS and/or cancer, MARINOL (delta-9-tetrahydrocannabinol) 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. Cannabinoids may still interact with other medications through both metabolic and pharmacodynamic mechanisms. Delta-9-tetrahydrocannabinol is highly 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 MARINOL to patients receiving other highly protein-bound drugs. Also, the literature contains evidence of drug interactions with smoked marijuana. The potential for drug interactions with MARINOL must be considered.

Drug-Drug Interactions

Published reports of drug/drug interactions involving cannabinoids are summarized in Table 1.

Table 1: Drug interaction information on delta-9-tetrahydrocannabinol

Concomitant Drug	Clinical Effect(s)
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Antipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive or super-additive tachycardia, drowsiness
Disulfiram	A reversible hypomanic reaction was reported in a 28 year old man who smoked marijuana; confirmed by dechallenge and rechallenge
Fluoxetine	A 21 year old female with depression and bulimia receiving 20 mg/day fluoxetine for 4 weeks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Theophylline	Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

Adults:

AIDS-related anorexia associated with weight loss:

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 mg before lunch and 5 mg before supper. 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.

Caution should be exercised in escalating the dosage of MARINOL because of the increased frequency of dose-related adverse experiences at higher dosages.

The pharmacologic effects of MARINOL are reversible upon treatment cessation.

Antiemetic in Cancer Chemotherapy-induced Nausea and Vomiting:
Evidence from clinical trials has shown that MARINOL is best administered at an initial dose of 5 mg/m^2, 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^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose.

Clinical practice experience suggests that a dosage of 5 mg three or four times daily may be adequate for most patients regarding efficacy and tolerability. 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. Caution should be exercised in escalating the dosage of MARINOL because of the increased frequency of dose-related adverse experiences at higher dosages (see Table 4, Clinical Trials). The pharmacologic effects of MARINOL are reversible upon treatment cessation.

Pediatrics: The safety and efficacy of MARINOL have not been established in adolescents or children under 18 years of age, therefore MARINOL should not be used in adolescents or children.

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. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

Missed Dose

If a dose is missed, patients should take it as soon as they remember. However, if it is almost time for the next dose, the missed dose should be skipped and the patient should go back to their regular dosing schedule. The dose should not be doubled.

OVERDOSAGE

Signs and symptoms following MILD MARINOL (delta-9-tetrahydrocannabinol) 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 delta-9-tetrahydrocannabinol is 30 mg/kg (2100 mg/70 kg). 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MARINOL (dronabinol) is an oral dosage form containing dronabinol which is synthetic delta-9-tetrahydrocannabinol. Delta-9-tetrahydrocannabinol is the main psychotropic component in *Cannabis sativa* (marijuana).

Delta-9-tetrahydrocannabinol is a cannabinoid receptor agonist. There are two known cannabinoid receptors, CB_1 and CB_2. CB_1 receptors are found in large quantities in the cerebral cortex, hippocampus, basal ganglia and cerebellum. Lower amounts are found in the hypothalamus and spinal cord. These locations can be used to predict the pharmacological effects of Delta-9-tetrahydrocannabinol. CB_1 receptors are not found in the respiratory centres of the brainstem, CB_2 receptors are found peripherally on immune cells.

Cannabinoids have been shown to stimulate appetite and reduce nausea and vomiting. Specifically, the endocannabinoid anandamide has been shown to stimulate food intake. Delta-9-tetrahydrocannabinol binds to the same cannabinoid receptor, thereby increasing appetite. In addition, delta-9-tetrahydrocannabinol and other cannabinoids have been shown to reduce emesis by binding to CB_1 receptors.

Pharmacodynamics:

Dronabinol has been shown to have psychotropic and antiemetic activity. Delta-9-tetrahydrocannabinol can produce changes in mood, decrease in cognitive performance and memory, decrease in ability to control drives and impulses, altered perception of reality, particularly altered time sense, and reversible effects on appetite. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability.

Animal data has shown that Delta-9-tetrahydrocannabinol has various effects on the central nervous system which are generally reported in the literature including analgesia, reduction of nausea and vomiting in cancer chemotherapy, reduction in intraocular pressure, appetite stimulation in wasting syndromes, relief from muscle spasms and spasticity in multiple sclerosis and decreased intestinal motility. Other effects of Delta-9-tetrahydrocannabinol include changes in cognitive ability and memory, dysphoria and/or euphoria as well as sedation.

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

After oral administration, delta-9-tetrahydrocannabinol 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 delta-9-tetrahydrocannabinol may continue for 24 hours or longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacologic effects of delta-9-tetrahydrocannabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic delta-9-tetrahydrocannabinol exposure, healthy male volunteers (N = 12) received 210 mg/day delta-9-tetrahydrocannabinol, administered orally in divided doses, for 16 days. An initial tachycardia induced by delta-9-tetrahydrocannabinol 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 delta-9-tetrahydrocannabinol 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

The single and multiple dose (twice daily for 10 days) pharmacokinetics of MARINOL and 11-OH-delta-THC, after administration of 2.5, 5 and 10 mg capsules, were assessed in healthy male and female volunteers. Results of this study are presented in Table 2 and 3. A slight increase in dose proportionality on mean Cmax and AUC (0-12) of dronabinol was observed with increasing dose over the dose range studied. Limited accumulation (range 1.18 to 2.43) of dronabinol was observed at all doses investigated.

Table 2: Summary of MARINOL's pharmacokinetic parameters in healthy volunteers. Arithmetic Mean (SD)

Dose	C_{max} (ng/mL)	Tmax (h)	$t_{½}$ (h)	$AUC_{0\rightarrow\infty}$	CL/F (L/h)
Single Dose					
2.5 mg	0.65 (0.304)	2.00 (0.50-4.00)	1.31 (0.659)	2.32 (2.472)	1676.20 (698.7)
5 mg	1.83 (1.429)	1.00 (0.50-3.00)	1.43 (0.490)	3.45 (2.684)	2847.84 (2678.0)
10 mg	6.22 (2.652)	1.50 (0.50-3.00)	4.37 (4.768)	9.67 (3.904)	1254.27 (657.2)
Dose	**C_{max} (ng/mL**	**Tmax (h)**	**$t_{½}$ (h)**	**$AUC_{0\rightarrow12}$**	**CL/F (L/h)**
Multiple Dose					
2.5 mg	1.32 (0.617)	1.00 (0.50-4.00)	16.69 (21.723)	2.88 (1.566)	1074.27 (449.9)
5 mg	2.96 (1.807)	2.50 (0.50-4.00)	43.27 (27.986)	6.16 (1.847)	926.15 (444.5)
10 mg	7.88 (4.544)	1.50 (0.50-3.50)	87.04 (22.645)	15.17 (5.516)	754.56 (300.0)

The different strengths of MARINOL are not bioequivalent to each other.

Table 3: Summary of 11-OH-THC's pharmacokinetic parameters in healthy volunteers. Arithmetic Mean (SD)

Dose	C_{max} (ng/mL)	Tmax (h)	$t_{½}$ (h)	$AUC_{0\rightarrow\infty}$
Single Dose				
2.5 mg	1.19 (0.763)	3.00 (0.77-4.00)	5.11 (2.719)	4.28 (2.629)
5 mg	2.23 (1.500)	2.00 (1.00-3.00)	6.58 (4.403)	8.03 (4.526)
10 mg	7.51 (5.264)	2.00 (1.00-3.50)	8.51 (1.606)	25.74 (15.156)
Dose	**C_{max} (ng/mL)**	**Tmax (h)**	**$t_{½}$ (h)**	**$AUC_{0\rightarrow12}$**
Multiple Dose				
2.5 mg	1.65 (0.752)	1.75 (0.50-4.00)	13.65 (9.232)	5.99 (2.459)
5 mg	3.84 (2.322)	2.50 (0.75-4.00)	14.38 (6.428)	12.59 (3.948)
10 mg	7.95 (3.167)	2.00 (0.75-3.50)	23.11 (11.289)	29.50 (9.909)

The different strengths of MARINOL are not bioequivalent to each other.

Absorption and Distribution: Delta-9-tetrahydrocannabinol is almost completely absorbed (90 to 95%) after single oral doses of MARINOL. 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. Delta-9-tetrahydrocannabinol 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. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

Metabolism: Delta-9-tetrahydrocannabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Delta-9-tetrahydrocannabinol 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 0.5 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.

Excretion: Delta-9-tetrahydrocannabinol and its biotransformation products are excreted in both faeces and urine. Biliary excretion is the major route of elimination with about half of a radio-labelled oral dose being recovered from the faeces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the faeces.

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

In a study of MARINOL Capsules 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 and Conditions

Pediatrics: The pharmacokinetic profile of MARINOL has not been investigated in pediatric patients.

Geriatrics: The pharmacokinetic profile of MARINOL has not been investigated in geriatric patients.

STORAGE AND STABILITY

MARINOL (delta-9-tetrahydrocannabinol) should be stored at
2° to 8° C, in well sealed HDPE containers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MARINOL (dronabinol) is available as a solution in sesame oil in soft gelatin capsules containing:

- 2.5 mg of delta-9-tetrahydrocannabinol in a white capsule (identified UM) in bottles containing 60 capsules
- 5.0 mg of delta-9-tetrahydrocannabinol in a brown capsule (identified UM) in bottles containing 60 capsules and
- 10.0 mg of delta-9-tetrahydrocannabinol in an orange capsule (identified UM) in bottles containing 60 capsules.

Non-medicinal ingredients: iron oxide red (5 and 10 mg), iron oxide black (5 mg), iron oxide yellow (10 mg), gelatin, glycerin, sesame oil, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

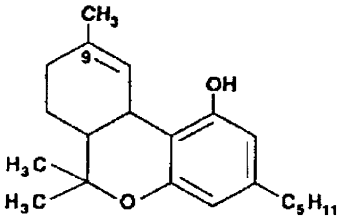
Delta-9-tetrahydrocannabinol is one of the principal psychoactive substances present in *Cannabis sativa*, *L.* (marijuana).

Proper name: dronabinol (synthetic delta-9-tetrahydrocannabinol)

Chemical name: (6a*R*-trans)-6a,7,8 10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6*H*-dibenzo[b,d]pyran-1-ol.

Molecular formula and molecular mass: $C_{21}H_{30}O_2$ 314.47

Structural Formula



Physicochemical properties: Delta-9-tetrahydrocannabinol in its raw form, is a clear to amber resin, sticky at room temperature and hard at refrigerated temperatures.

Solubility: It is highly lipid soluble and can be dissolved slightly in aqueous solutions (in the range of a few mg/mL).

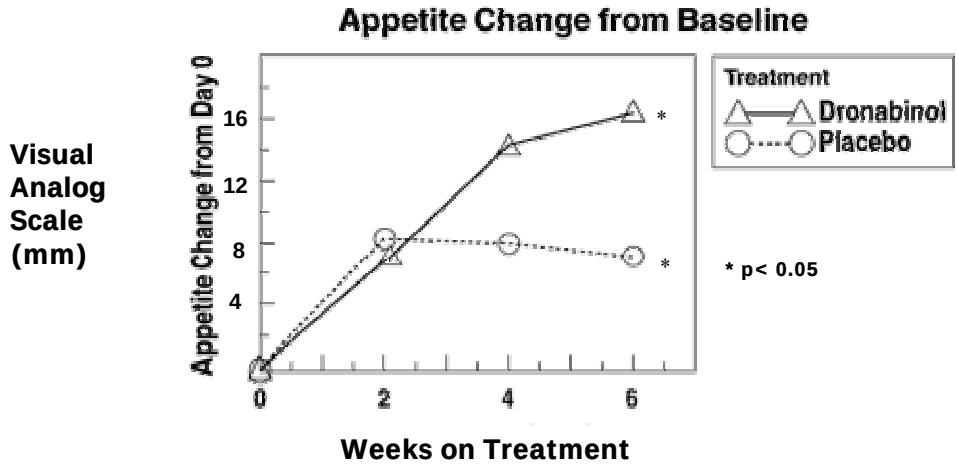
pK_a: Delta-9-tetrahydrocannabinol has a pK_a of 10.6.

Partition coefficient: The octanol/water partition ratio is approximately 6000:1 at pH 7.

CLINICAL TRIALS

AIDS-related anorexia associated with weight loss

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 12 month open-label study, in which there was a sustained improvement in appetite.

Antiemetic in cancer chemotherapy-induced nausea and vomiting

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). Escalating the MARINOL dose

above 7 mg/m² increased the frequency of adverse experiences, with no additional antiemetic benefit.

Table 4: 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/m2	36	32	32	23	65	12
> 7 mg/m2	33	31	36	13	58	28

* Nondysphoric events consisted of drowsiness, tachycardia, etc.

DETAILED PHARMACOLOGY

Animal Pharmacology

Most of the pharmacological effects reported in the literature describe the effects of pure Δ^9-THC, although other psychoactive cannabinoids have also been utilized.

In most animal species, Δ^9-THC produces a decrease in spontaneous activity, hypothermia, ataxia and hypersensitivity to tactile and auditory stimuli. With increasing doses, the intensity of these effects becomes more pronounced. In mice and rats, Δ^9-THC possesses anticonvulsant and weak antinociceptive activity. Aggressive behavior is decreased in nonstressed animals but is enhanced in stressed ones. Food and water intake is often decreased with a consequent weight loss. This latter observation differs from that seen in human subjects, probably due to the larger doses utilized in animals.

Δ^9-THC is not reinforcing in the monkey self-administration paradigm. The compound possesses discriminative stimulus properties and is interchangeable with Δ^8-THC and the 11-hydroxy metabolites. Δ^9-THC disrupts various reinforcement schedules of behavior as well as maze learning; these effects are consistent with its disruptive effect in humans on time estimation and short-term memory, respectively.

Studies, evaluating the potential interaction of Δ^9-THC and several neurotransmitters, namely ACh, NE, ΔA and 5-HT, are contradictory but present evidence indicates that these neurotransmitters may not be primarily involved in the action of cannabinoids on the CNS. However, the effects of Δ^9-THC on the brain are produced in nanomolar concentrations and are stereospecific. Such properties are characteristic of drugs that act on or close to receptor sites. Specific receptors for Δ^9-THC have not been isolated.

A remarkable degree of tolerance develops to the effects of Δ^9-THC and other psychoactive cannabinoids. This tolerance has been confirmed by many laboratories and occurs in most species, including human beings. There is cross-tolerance with other cannabinoids but not with narcotics.

Chronic exposure to fairly high doses of Δ^9-THC produces a dose-related depression of

ovarian function, decreases in concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and anovulatory cycles. Attenuated levels of testosterone, decreased spermatogenesis and Leydig cell regression have also been reported.

TOXICOLOGY

Acute Toxicity

Species	Strain	Route of Administration	LD50 mg/kg	Reference
Mouse	Swiss Webster (M)	i.v.	60	Harris (1971)
		i.p.	168	Dewey et al (1972)
		p.o.	1900	
Rat	Sprague Dawley (M)	i.v.	100	Harris (1971)
		i.p.	430	Dewey et al (1972)
		p.o.	>2000	
	Fisher (M)	p.o.	1910	Thompson et al (1973)
	(F)	p.o.	1040	
Monkey		p.o.	>1313	Thompson et al (1973)
Dog		p.o.	>3000	Thompson et al (1973)

The acute toxicity of Δ^9-THC is low. The compound induces decreased activity, ataxia, catatonia, hypothermia, hypersensitivity to touch, decreased respiratory rate and generalized body twitching. Death appeared to be due to respiratory arrest.

Subacute toxicity

- Δ^9-THC was administered orally to rats in a dose range of 62.5-1000 mg/kg over a 5-day period. The clinical signs were similar to those seen in the acute toxicity studies. At a dose of 250 mg/kg, Δ^9-THC was well tolerated. Tolerance to the effects of Δ^9-THC developed rapidly as evidenced by less severe symptoms and a more rapid recovery. Depression of weight gain and organ weight changes (increased adrenal and liver weights, decreased spleen weight) occurred in all treated groups. Hypocellularity of the bone marrow and atrophy of splenic germinal centers were observed when doses >500 mg/kg were administered.

- Δ^9-THC was administered orally to monkeys at doses up to 5 g/kg over a 7-day period. Pharmacotoxic signs were similar to those seen in rats. In addition, anorexia and constipation also occurred. No mortality was seen even at the highest dose although it is questionable whether such large quantities were absorbed because the pharmacotoxic signs did not increase with increasing doses. Bone marrow hypocellularity was observed in this species too.

Chronic toxicity

- Δ^9-THC was administered orally to rats at doses of 50, 250, 400 and 500 mg/kg/day for 119 days. Twenty rats/sex were treated with the two lower doses and 30 rats/sex were treated with the two higher doses. Pharmacotoxic signs were seen at all doses. Initially, they included behavioural depression, hypothermia, sedation, ataxia,

hypersensitivity to touch, hypopnoea and decreased weight gain. During the study, CNS depression was replaced by CNS stimulation as evidenced by hyperactivity, irritability, aggression (fighting behaviour), tremors and convulsions. Tremors and convulsions occurred at the high doses and were dose and treatment duration related. Tolerance to convulsions did not develop. Depressed weight gain was present throughout the study. Clinical chemistry revealed elevated SGOT, SGPT and glucose levels and haematological examinations indicated increased red blood cell counts and haematocrit values. Adrenal weights were increased in groups treated with all the doses of Δ^9-THC, attenuated pancreas, pituitary and uterus weights were seen only in the groups that received 400 or 500 mg/kg. Histopathological changes included hypocellularity of the bone marrow and spleen, necrosis and vacuolization of the adrenal cortex. These changes were noted at doses of 250 mg/kg and higher.

- Δ^9-THC was also administered to rats for 180 days, at doses of 2, 10 and 50 mg/kg/day. However, there were too few rats in the study (4/sex/group) to reach meaningful conclusions.

Carcinogenicity

Carcinogenicity studies in mice and rats have been conducted under the US National Toxicology Program (NTP). There was no evidence of carcinogenicity in rats administered up to 50 mg/kg/day (125 times the maximum recommended human dose based on a 50-kg individual) of delta-9-tetrahydrocannabinol orally for two years. Male and female mice administered 125 mg/kg/day (312 times the maximum recommended human dose) of delta-9-tetrahydrocannabinol for two years showed an increased incidence of thyroid gland follicular cell adenoma, which was not observed in mice administered 250 or 500 mg/kg/day (625 and 1250 times, respectively, the maximum recommended human dose). The findings in mice were interpreted as "equivocal" by NTP, based on a lack of a dose-response relationship; that is, based on a marginal increase of neoplasms that may be study drug related. The significance of these findings to humans is unknown.

Delta-9-tetrahydrocannabinol was not genotoxic in the Ames tests, the in vitro chromosomal aberration test in Chinese hamster ovary cells, and the in vivo mouse micronucleus test. It, however, produced a weak positive response in a sister chromatid exchange test in Chinese hamster ovary cells.

Reproduction Studies

- Male and female rats (10 and 20, respectively, per group) received 0, 0.5, 1.5 and 5 mg/kg of Δ^9-THC by gavage. The male animals were treated for 60 days prior to mating. The female animals were treated for two weeks prior to mating and during pregnancy and lactation. Treatment had little effect on the number of corpora lutea, implantation sites, resorption and viable fetuses. At day 12 of lactation and at weaning a dose-related decrease in the survival of offsprings was observed in those groups where the mothers were treated with the 1.5 and 5 mg/kg doses.

- Teratology studies were carried out in both rats and rabbits. The rats were treated with 0, 5, 15 and 50 mg/kg of Δ^9-THC, while the rabbits were treated with 0, 0.5, 1.5, 5 and 15 mg/kg of Δ^9-THC. Three high dose fetuses in the rabbit study showed external abnormalities (talipomanus) and 1/3 fetus had multiple anomalies (acrania, spina bifida). Pup weight and survival rate were within the normal range in all groups.

- In further reproduction and teratology studies, rats and mice were treated with Δ^9-THC at doses ranging from 12.5-50 mg/kg and 150-600 mg/kg, respectively. In these studies, Δ^9-THC increased the number of early resorptions, increased fetal mortality and decreased the number of viable pups. Teratogenic effects were not seen.

- At 240 mg/kg, Δ^9-THC was teratogenic in mice, causing orofacial anomalies (cleft palate, cleft lips and open eyelids).

- In young male rats, 77 days of treatment with Δ^9-THC (5-25 mg/kg/day) produced the following changes: decreased prostate, epididymal and seminal vesicle weights and a decrease in seminal fluid volume. At 25 mg/kg, Δ^9-THC produced an area of sparse Leydig cells in the interstitium of testis, a decrease in spermatogenesis and in the number of developing germ cells in the seminiferous tubules. However, it did not affect sperm count, serum testosterone levels, mating and the weight of the offsprings.

Special Studies

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

REFERENCES

Artim R and DiBella N: Tetrahydrocannabinol (THC) plus prochloroperazine (PCZ) for refractory
nausea and vomiting (N/V). Proc Am Soc Clin Oncol 2:84, 1983 (abstr C-330)

Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995;10(2):89-97.

Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage 1997;14(1):7-14.

Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Simon RM, and Rosenberg SA: Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate. A prospective randomized evaluation. Ann Intern Med 91:819-824, 1979

Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, and Rosenberg SA: A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. Cancer 47:1746-1751, 1981

Citron ML, Herman TS, Vreeland F, Krasnow SH, Fossieck Jr BE, Harwood S, Franklin R and Cohen MH: Antiemetic efficacy of levonantradol compared to delta-9-tetrahydocannabinol for chemotherapy-induced nausea and vomiting. Cancer Treat Reports 69:109-112, 1985

Colls BM, Ferry DG, Gray AJ, Harvey VJ and McQueens EG: The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. N Zealand Med J 1980;41:449-451.

Compton DR, Rice KC, De Costa BR, Razdan RK, Melvin LS, Johnson MR et al. Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities. J Pharmcol Exp Ther 1993;265(1):218-26.

Darmani NA, Sim-Selley LJ, Martin BR et al. Antiemetic and motor-depressive actions of CP55,940 : cannabinoid CB1 receptor characterization, distribution, and G-protein activation. Eur J Pharmacol 2003;459;83-95.

Darmani NA. Delta-9-tetrahydrocannabinoid CB1 receptors in the least shrew. Pharmacol Biochem Behav 2001;69:239-249.

Darmani NA. Delta-9-tetrahydrocannabinol and synthetic cannabinoids prevent emesis

produced by the cannabinoid CB1 receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacolgy 2001;24:198-203.

Darmani NA. The cannabinoid CB1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55,212-2. Eur J Pharmacol 2001;430:49-58.

Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34(5):605-13.

Dewey WL, Harris LS and Kennedy JS: Some pharmacological and toxicological effects of 1-trans-delta 8-, and 1-trans-delta 9-tetrahydrocannabinol in laboratory rodents. Arch Int Pharmacodyn 196:133-145, 1972

DiMarzo V, Goparaju SK, Wang L et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 2001;410:822-25.

Ekert H, Waters KD, Jurk IH, Mobilia J and Loughnan P: Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Australia 2: 657-659, 1979

Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ and Schutt A: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Ann Intern Med 91:825-830, 1979.

Garb S, Beers Jr AL, Bograd M, McMahon RT, Mangalik A, Ashmann AC and Levine S: Two-pronged study of tetrahydrocannabinol (THC) prevention of vomiting from cancer chemotherapy. IRCS Medical Science 8:203-204, 1980

Gralla RJ, Tyson LB, Borden LA, Clark RA, Kelsen DP, Kris MG, Kalman LB and Groshen S: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. Cancer Treat Reports 68:163-172, 1984

Harris LS: Cannabis: A review of progress. In: Lipton MA, DiMascio A and Killam KF (eds) Psychopharmacology: A generation of progress. Raven Press, New York, pp 1565-1574, 1978

Harris LS: General and behavioral pharmacology. Pharmacol Rev 23:285-294, 1971

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, De Costa BR et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci 1990;87:1932-1936.

Homesley HD, Gainey J, Jobson VW, Spur C, Welander CE, Muss HB and Kimball J:

Failure of delta-9-tetracannabinol and prochlorperazine to control chemotherapy induced nausea and vomiting. Proc Am Soc Clin Oncol 2:67, 1982 (abstr C-260)

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54:161-202.

Jaffe JH: Drug addiction and drug abuse. In: Goodman LS and Gilman A (eds) The pharmacological basis of therapeutics. MacMillan Publishing Co. Inc, pp 535-585, 1980

Kluin-Nelemans JC, Nelemans FA, Meuwissen OJ and Maes RAA: Delta-9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancer chemotherapy: A double blind crossover trial against placebo. Vet and Human Tox 21:338-340, 1979.

Laszlo J, Lucas VS. Delta-9-tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. JAMA 1980;243(12):1241-1243.

Levitt M, Faiman C, Hawks R and Wilson A: Randomized double blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. Proc Am Soc Clin Oncol 3:91, 1984 (abstr C-354)

Levitt M, Wilson A, Bowman D, Faiman C, Kemel S, Krepart G, Schipper H, Weinerman B andWeinerman R: Dose vs response of tetrahydrocannabinol (THC) vs prochlorperazine (PCPZ) as chemotherapy antiemetics. Proc Am Soc Clin Oncol 22:422, 1981 (abstr C-352)

Lucas VS Jr and Laszlo J: Delta-9-tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. JAMA 243:1241-1243, 1980

Martin BR. Identification of the endogenous cannabinoid system through integrative pharmacological approaches. J Pharmacol Exp Ther 2002;301(3):790-6.

McCabe M, Smith FP, Goldberg D, Macdonald J, Woolley PV, Warren R, Brodeur R and Schein PS: Comparative trial of oral delta-9-tetracannabinol (THC) and prochlorperazine (PCZ) for cancer chemotherapy-related nausea and vomiting. Proc Am Soc Clin Oncol 22:416, 1981 (abstr C-331)

Mendelson JH: Marijuana. In: Meltzer HY (ed) Psychopharmacology: The third generation of progress. Raven Press, New York, pp 1565-1571, 1987

Meyer RE: Behavioral pharmacology of marijuana. In: Lipton MA, DiMascio A and Killam KF (eds) Psychopharmacology: A generation of progress. Raven Press, New York, pp 1639-1652, 1978

Meyers F, Stanton W, Dow G and Rocchio G: Reduced adverse effects with optimal antiemetic dosage of delta-9-tetrahydrocannabinol (THC). Proc Am Soc Clin Oncol 3:94, 1984 (abstr C-366)

Monro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365(6441):61-5.

Nahas GG: Cannabis: toxicological properties and epidemiological aspects. Med J Australia 145:82-87, 1986

Orr LE, McKernan JF and Bloome B: Antiemetic effect of tetrahydrocannabinol compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Arch Intern Med 140:1431-1433,1980

Ostenson R, Roffman R, Kopecky K, and Dunner D: Antiemetic effects of delta-9-tetrahydrocannabinol (THC) in patients receiving chemotherapy. Proc 13th Intern Cancer Congr, Seattle, Washington, 1982 (abstr 04016)

Pertwee RG. Pharmacology of cannabinoid receptor ligands. Curr Med Chem 1999;6(8):635-64.

Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy Martinez S et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994;350(2-3):240-4.

Sallan MD, Cronin C, Zelen M and Zinberg NE: Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochloroperazine. New Engl J Med 302:135-138, 1980

Sallan SE, Zinberg MD and Frei III E: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer therapy. New Engl J Med 293(16):795-797, 1975

Stanton W: Antiemetic efficacy and safety of delta-9-tetrahydrocannabinol (THC): Effect of dose and anticancer regimen. Proc Am Soc Clin Oncol 2:94, 1983 (abstr C-365)

Sweet DL, Miller NJ, Weddington W, Senay E and Sushelsky L: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A pilot study. J Clin Pharmacol 21:70S-75S, 1981

Thompson GR, Rosenkrantz H, Schaeppi UH and Baude MC. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. Toxicol Appl Pharmacol 25:363-372, 1973

Ungerleider JT Andrysiak T: Therapeutic issues of marijuana and THC (tetrahydrocannabinol). Int J Addiction 20:691-699, 1985

Ungerleider JT, Fairbanks LA, Andrysiak T, Sarna G, Goodnight J and Jamison K: THC or Compazine for the cancer chemotherapy patient - the UCLA study. Part II: Patient drug preference. Am J Clin Oncol 8:142-147, 1985.

PART III: CONSUMER INFORMATION

[N]MARINOL®
dronabinol;
delta-9-tetrahydrocannabinol

This leaflet is part III of a three-part "Product Monograph" published when MARINOL was approved for sale in Canada and is designed specifically for Consumers. Please read it and keep it with your medicines in case you need to look at it again. This leaflet is a summary and will not tell you everything about MARINOL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MARINOL is intended to:

- help regain the loss of appetite associated with weight loss in patients with AIDS
- prevent nausea (feeling of sickness) and vomiting, which can occur while undergoing cancer chemotherapy treatment.

What it does:
MARINOL increases appetite and decreases nausea (feeling of sickness) and vomiting.

When it should not be used:

If you have any of the following conditions, you should **not** use this product:

- known or suspected allergy to marijuana, other cannabinoids, or sesame oil
- significant liver or kidney problems
- serious heart disease
- history of schizophrenia or any other psychotic disorder
- in children or adolescents under 18 years of age.
- are pregnant or nursing
- are female at risk of pregnancy and not using a reliable contraceptive
- are male and intending to father a child while on treatment with MARINOL

What the medicinal ingredient is:
MARINOL contains delta-9-tetrahydrocannabinol (THC), which is a synthetic form of the naturally occurring THC in Cannabis sativa L. (marijuana).

What the important nonmedicinal ingredients are:
sesame seed oil
Other non-medicinal ingredients include: gelatin, glycerin, iron oxide black (5 mg capsules), iron oxide red (5 and 10 mg capsules), iron oxide yellow (10 mg capsules) and titanium dioxide.

What dosage forms it comes in:
2.5 mg, 5 mg and 10 mg capsules

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

THC, the active component of MARINOL, has numerous effects on the central nervous system such as changes in mood, decreased mental performance and memory and altered perceptions of reality. Symptoms such as fainting and interference in the physical ability to carry out complicated tasks have been seen in patients taking MARINOL. Therefore you should not drive, operate machinery or engage in activities that require unimpaired judgement and coordination.

While taking MARINOL you should not drink alcohol or take other drugs which may have an effect on the central nervous system such as sedatives or hypnotics, without consulting your doctor, as these products have a further additive effect on some of the effects listed above.

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

BEFORE you use MARINOL talk to your doctor or pharmacist if you:

- suffer from any allergic reactions
- suffer from epilepsy
- suffer from any liver, kidney or heart disease
- suffer from schizophrenia or depression
- have an irregular heart beat/rhythm, including a fast or slow pulse
- have high blood pressure
- have abused or are abusing drugs or alcohol
- are taking other prescription medicines, over-the-counter medicines or natural health products.

You and your partner must ensure reliable contraceptive precautions are taken during your treatment and for at least three months after you stop taking MARINOL.

There may be a potential for abuse or development of dependence in some individuals with long-term use. Discuss with your doctor.

If you see another doctor or go into hospital, let them know what medicines you are taking.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with MARINOL include: alcohol, amitriptyline, amoxapine, amphetamines, antihistamines, antipyrine, atropine, barbituates, benzodiazepines, buspirone, CNS depressants, disulfiram, cocaine, desipramine, fluoxetine, lithium, muscle relaxants, opioids, scopolamine, sleeping pills, theophylline, tricyclic antidepressants.

Care should be taken with sedatives and hypnotics as co-administration with MARINOL may possibly enhance the effect.

Do not smoke or use other forms of cannabis while using MARINOL since it can cause an overdose.

Alcohol may interact with MARINOL, particularly in affecting coordination, concentration and the ability to respond quickly.

PROPER USE OF THIS MEDICATION

MARINOL must be swallowed whole to work effectively. Do not crush or chew the capsules.

MARINOL should be taken exactly as directed by your doctor.

Your doctor must write a new prescription each time you need more MARINOL. It is important to call your doctor before you take your last capsule. You should also give your pharmacist a few days notice of your need for more MARINOL.

Your doctor has prescribed this drug for your use only. Do not let anyone else use it.

Usual starting dose:
One white capsule (2.5 mg) of MARINOL twice daily, before lunch and supper.

Dose adjustments:
Your doctor may adjust your MARINOL dosage if needed to maximize its effect or to decrease any side effects.

Overdose:
- Signs of a **mild** overdose would include drowsiness, euphoria, heightened sensory awareness, altered time perception, red eyes, dry mouth and rapid heart rate (tachycardia).
- **Moderate** overdosage would produce memory problems, depersonalization, mood alteration, urinary retention, and constipation.
- **Severe** overdosage would lead to decreased motor coordination, lethargy, slurred speech, and dizziness when standing up too fast (postural hypotension).
- An overdose might cause you to faint.

If you accidentally take more than you normally do and you experience severe intoxication reactions, contact your nearest hospital emergency department, or tell your doctor immediately. Bring any remaining medicine with you.

Missed Dose:

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you notice any symptoms that bother you, stop the MARINOL and call your doctor at once.

If You Have Problems in the First Few Days
When you first use MARINOL your body is more sensitive and you may experience dizziness, confusion, sleepiness, or a high feeling. These symptoms usually go away in 1 to 3 days with continued dosage. If these symptoms are troublesome or persist, notify your doctor at once. Your doctor may then reduce the dose to one capsule before supper, or later in the evening, or even at bedtime.

What to Do When Problems Occur
IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROBLEMS, STOP THE MARINOL AND CALL YOUR DOCTOR AT ONCE.

You may experience changes in mood or have other effects such as euphoria, dizziness, somnolence and thinking abnormalities, when taking MARINOL. Be sure that there is a responsible person nearby when you first take MARINOL or when there is an adjustment in your dose. MARINOL may produce physical and psychological dependence.

You may also experience uncommon side effects such as feeling tired, dry mouth or allergic reactions (e.g. rash, itchiness).

You should not smoke marijuana while using MARINOL. It is possible to get too much delta-9-tetrahydrocannabinol (an overdose), especially if you use MARINOL and smoke marijuana at the same time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	anxiety	√		
	confusion	√		
	dizziness	√		
	drowsiness	√		
	feeling abnormal		√	
	hallucination			√
	palpitations			√
	paranoia			√
Un-common	depression		√	
	hypotension			√
	seizure			√
	fall		√	

This is not a complete list of side effects. For any unexpected effects while taking MARINOL, contact your doctor or pharmacist.

HOW TO STORE IT

Store in a cool place (between 2° and 8°C), in the original container.

Be careful that the capsules don't freeze. Heat or moisture may cause your MARINOL to break down or stick together. Keep your medicine away from heat, direct light and damp places like the bathroom or near the kitchen sink or stove.

Keep MARINOL out of the reach of children. If a child puts a capsule in their mouth or swallows MARINOL, take the medicine away from the child and contact a poison control centre immediately, or contact a doctor immediately.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.solvaypharma.ca or by contacting the sponsor, Solvay Pharma, at: 1-800-268-4276

This leaflet was prepared by Solvay Pharma

Last revised:

May 4, 2007