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MARINOL[®] **ⒸIII**
(dronabinol)
Capsules
R_x only

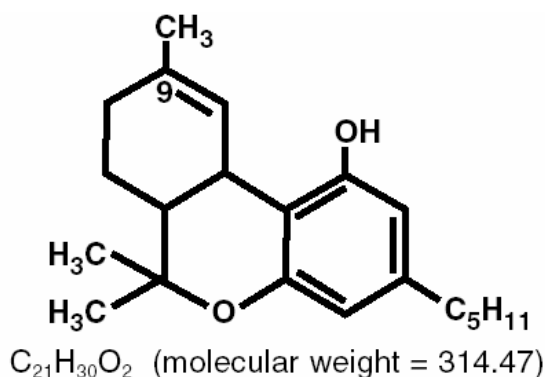
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7 **DESCRIPTION**

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



11

12 Dronabinol, the active ingredient in MARINOL[®] (dronabinol) Capsules, is synthetic
 13 delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a
 14 naturally occurring component of *Cannabis sativa L.* (Marijuana).

15

16 Dronabinol is a light yellow resinous oil that is sticky at room temperature and
 17 hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame
 18 oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

19

20 Capsules for oral administration: MARINOL Capsules is supplied as round, soft
 21 gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each MARINOL
 22 Capsule strength is formulated with the following inactive ingredients: 2.5 mg capsule
 23 contains gelatin, glycerin, sesame oil, and titanium dioxide; 5 mg capsule contains iron
 24 oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; 10 mg
 25 capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil, and
 26 titanium dioxide.

27

28 **CLINICAL PHARMACOLOGY**

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

33

34 **Pharmacodynamics**

35 Dronabinol-induced sympathomimetic activity may result in tachycardia and/or
36 conjunctival injection. Its effects on blood pressure are inconsistent, but occasional
37 subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing.
38

39 Dronabinol also demonstrates reversible effects on appetite, mood, cognition,
40 memory, and perception. These phenomena appear to be dose-related, increasing in
41 frequency with higher dosages, and subject to great interpatient variability.
42

43 After oral administration, dronabinol has an onset of action of approximately 0.5 to 1
44 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6
45 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer
46 after administration.
47

48 Tachyphylaxis and tolerance develop to some of the pharmacologic effects of
49 dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on
50 sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol
51 exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol,
52 administered orally in divided doses, for 16 days. An initial tachycardia induced by
53 dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A
54 decrease in supine blood pressure, made worse by standing, was also observed initially.
55 These volunteers developed tolerance to the cardiovascular and subjective adverse CNS
56 effects of dronabinol within 12 days of treatment initiation.
57

58 Tachyphylaxis and tolerance do not, however, appear to develop to the appetite
59 stimulant effect of MARINOL Capsules. In studies involving patients with Acquired
60 Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of MARINOL
61 Capsules has been sustained for up to five months in clinical trials, at dosages ranging
62 from 2.5 mg/day to 20 mg/day.
63

64 **Pharmacokinetics**

65 **Absorption and Distribution:** MARINOL Capsules is almost completely absorbed
66 (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic
67 metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the
68 systemic circulation. Dronabinol has a large apparent volume of distribution,
69 approximately 10 L/kg, because of its lipid solubility. The plasma protein binding of
70 dronabinol and its metabolites is approximately 97%.
71

72 The elimination phase of dronabinol can be described using a two compartment
73 model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25
74 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites
75 may be excreted at low levels for prolonged periods of time.
76

77 The pharmacokinetics of dronabinol after single doses (2.5, 5, and 10 mg) and
78 multiple doses (2.5, 5, and 10 mg given twice a day; BID) have been studied in healthy
79 women and men.
80

81 **Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol**
 82 **in Healthy Volunteers (n=34; 20-45 years) under Fasted Conditions**
 83

Mean (SD) PK Parameter Values			
BID Dose	Cmax ng/mL	Median Tmax (range), hr	AUC(0-12) ng•hr/mL
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

84
 85 A slight increase in dose proportionality on mean Cmax and AUC(0-12) of
 86 dronabinol was observed with increasing dose over the dose range studied.
 87

88 **Metabolism:** Dronabinol undergoes extensive first-pass hepatic metabolism, primarily
 89 by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol
 90 and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately
 91 equal concentrations in plasma. Concentrations of both parent drug and metabolite peak
 92 at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values
 93 for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of
 94 cannabinoid distribution.
 95

96 **Elimination:** Dronabinol and its biotransformation products are excreted in both feces
 97 and urine. Biliary excretion is the major route of elimination with about half of a radio-
 98 labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to
 99 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the
 100 feces.
 101

102 Following single dose administration, low levels of dronabinol metabolites have been
 103 detected for more than 5 weeks in the urine and feces.
 104

105 In a study of MARINOL Capsules involving AIDS patients, urinary
 106 cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week
 107 period. The urinary cannabinoid/creatinine ratio was closely correlated with dose. No
 108 increase in the cannabinoid/creatinine ratio was observed after the first two weeks of
 109 treatment, indicating that steady-state cannabinoid levels had been reached. This
 110 conclusion is consistent with predictions based on the observed terminal half-life of
 111 dronabinol.
 112

113 **Special Populations:** The pharmacokinetic profile of MARINOL Capsules has not
 114 been investigated in either pediatric or geriatric patients.
 115

116 **Clinical Trials**

117 **Appetite Stimulation:** The appetite stimulant effect of MARINOL Capsules in the
 118 treatment of AIDS-related anorexia associated with weight loss was studied in a
 119 randomized, double-blind, placebo-controlled study involving 139 patients. The initial
 120 dosage of MARINOL Capsules in all patients was 5 mg/day, administered in doses of 2.5

121 mg one hour before lunch and one hour before supper. In pilot studies, early morning
 122 administration of MARINOL Capsules appeared to have been associated with an
 123 increased frequency of adverse experiences, as compared to dosing later in the day. The
 124 effect of MARINOL Capsules on appetite, weight, mood, and nausea was measured at
 125 scheduled intervals during the six-week treatment period. Side effects (feeling high,
 126 dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage
 127 level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper
 128 or bedtime.

129

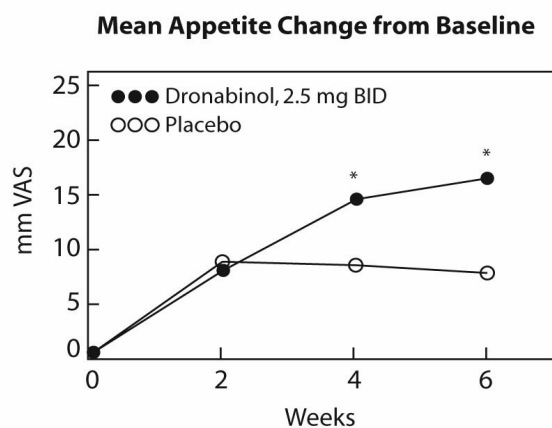
130 Of the 112 patients that completed at least 2 visits in the randomized, double-blind,
 131 placebo-controlled study, 99 patients had appetite data at 4-weeks (50 received
 132 MARINOL and 49 received placebo) and 91 patients had appetite data at 6-weeks (46
 133 received MARINOL and 45 received placebo). A statistically significant difference
 134 between MARINOL Capsules and placebo was seen in appetite as measured by the visual
 135 analog scale at weeks 4 and 6 (see figure). Trends toward improved body weight and
 136 mood, and decreases in nausea were also seen.

137

138

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

142



143

144 **Antiemetic:** MARINOL Capsules treatment of chemotherapy-induced emesis was
 145 evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of
 146 various malignancies. The antiemetic efficacy of MARINOL Capsules was greatest in
 147 patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's
 148 lymphomas. MARINOL Capsules dosages ranged from 2.5 mg/day to 40 mg/day,
 149 administered in equally divided doses every four to six hours (four times daily). As
 150 indicated in the following table, escalating the MARINOL Capsules dose above 7 mg/m²
 151 increased the frequency of adverse experiences, with no additional antiemetic benefit.

152

153

154

MARINOL Capsules Dose: Response Frequency and Adverse Experiences*
 (N = 750 treatment courses)

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

155 *Nondysphoric events consisted of drowsiness, tachycardia, etc.
156

157 Combination antiemetic therapy with MARINOL Capsules and a phenothiazine
158 (prochlorperazine) may result in synergistic or additive antiemetic effects and attenuate
159 the toxicities associated with each of the agents.
160

161 **INDIVIDUALIZATION OF DOSAGES**

162 The pharmacologic effects of MARINOL Capsules are dose-related and subject to
163 considerable interpatient variability. Therefore, dosage individualization is critical in
164 achieving the maximum benefit of MARINOL Capsules treatment.
165

166 ***Appetite Stimulation:*** In the clinical trials, the majority of patients were treated with
167 5 mg/day MARINOL Capsules, although the dosages ranged from 2.5 to 20 mg/day. For
168 an adult:

- 169 1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling
170 high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days
171 with continued dosage.
172
- 173 2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If
174 symptoms continue to be a problem, taking the single dose in the evening or at
175 bedtime may reduce their severity.
176
- 177 3. When adverse effects are absent or minimal and further therapeutic effect is desired,
178 increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg.
179 Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been
180 tolerated in about half of the patients in appetite stimulation studies.
181

182 The pharmacologic effects of MARINOL Capsules are reversible upon treatment
183 cessation.
184

185 ***Antiemetic:*** Most patients respond to 5 mg three or four times daily. Dosage may be
186 escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results.
187 Therapy should be initiated at the lowest recommended dosage and titrated to clinical
188 response. Administration of MARINOL Capsules with phenothiazines, such as
189 prochlorperazine, has resulted in improved efficacy as compared to either drug alone,
190 without additional toxicity.
191

192 ***Pediatrics:*** MARINOL Capsules is not recommended for AIDS-related anorexia in
193 pediatric patients because it has not been studied in this population. The pediatric dosage
194 for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is

195 recommended in prescribing MARINOL Capsules for children because of the
196 psychoactive effects.

197

198 **Geriatrics:** Caution is advised in prescribing MARINOL Capsules in elderly patients
199 because they may be more sensitive to the neurological, psychoactive and postural
200 hypotensive effects of the drug. In general, dose selection for an elderly patient should be
201 cautious, usually starting at the low end of the dosing range (**See PRECAUTIONS.**)

202

203 MARINOL Capsules should be used with caution when administered to elderly patients
204 with dementia, who are at increased risk for falls as a result of their underlying disease
205 state which may be exacerbated by the central nervous system effects of somnolence and
206 dizziness associated with MARINOL Capsules. These patients should be monitored
207 closely and placed on fall precautions prior to initiating MARINOL therapy. In
208 antiemetic studies, no difference in efficacy was apparent in patients >55 years old.

209

210 **INDICATIONS AND USAGE**

211 MARINOL Capsules is indicated for the treatment of:

212

1. anorexia associated with weight loss in patients with AIDS; and

213

214 2. nausea and vomiting associated with cancer chemotherapy in patients who have failed
215 to respond adequately to conventional antiemetic treatments.

216

217 **CONTRAINDICATIONS**

218 MARINOL Capsules is contraindicated in any patient who has a known sensitivity to
219 MARINOL Capsules or any of its ingredients. It contains cannabinoid and sesame oil and
220 should never be used by patients allergic to these substances.

221

222 **WARNINGS**

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

226

227 **PRECAUTIONS**

228 **General:** The risk/benefit ratio of MARINOL Capsules use should be carefully
229 evaluated in patients with the following medical conditions because of individual
230 variation in response and tolerance to the effects of MARINOL Capsules.

231

232 Seizure and seizure-like activity have been reported in patients receiving MARINOL
233 Capsules during marketed use of the drug and in clinical trials. (**See ADVERSE**
234 **REACTIONS** and **OVERDOSAGE.**) MARINOL Capsules should be used with caution
235 in patients with a history of seizure disorder because MARINOL Capsules may lower the
236 seizure threshold. A causal relationship between MARINOL Capsules and these events
237 has not been established. MARINOL Capsules should be discontinued immediately in
238 patients who develop seizures and medical attention should be sought immediately.

239

240 MARINOL Capsules should be used with caution in patients with cardiac disorders
241 because of occasional hypotension, possible hypertension, syncope, or tachycardia. (See
242 **CLINICAL PHARMACOLOGY**.)
243

244 MARINOL Capsules should be used with caution in patients with a history of
245 substance abuse, including alcohol abuse or dependence, because they may be more
246 prone to abuse MARINOL Capsules as well. Multiple substance abuse is common and
247 marijuana, which contains the same active compound, is a frequently abused substance.
248

249 MARINOL Capsules should be used with caution and careful psychiatric monitoring
250 in patients with mania, depression, or schizophrenia because MARINOL Capsules may
251 exacerbate these illnesses.
252

253 MARINOL Capsules should be used with caution in patients receiving concomitant
254 therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for
255 additive or synergistic CNS effects.
256

257 MARINOL Capsules should be used with caution in elderly patients because they
258 may be more sensitive to the neurological, psychoactive, and postural hypotensive effects
259 of the drug. (See **INDIVIDUALIZATION OF DOSAGES**.)
260

261 MARINOL Capsules should be used with caution in pregnant patients, nursing
262 mothers, or pediatric patients because it has not been studied in these patient populations.
263

264 **Information for Patients:** Patients receiving treatment with MARINOL Capsules
265 should be alerted to the potential for additive central nervous system depression if
266 MARINOL Capsules is used concomitantly with alcohol or other CNS depressants such
267 as benzodiazepines and barbiturates.
268

269 Patients receiving treatment with MARINOL Capsules should be specifically warned
270 not to drive, operate machinery, or engage in any hazardous activity until it is established
271 that they are able to tolerate the drug and to perform such tasks safely.
272

273 Patients using MARINOL Capsules should be advised of possible changes in mood
274 and other adverse behavioral effects of the drug so as to avoid panic in the event of such
275 manifestations. Patients should remain under the supervision of a responsible adult during
276 initial use of MARINOL Capsules and following dosage adjustments.
277

278 **Drug Interactions:** In studies involving patients with AIDS and/or cancer, MARINOL
279 Capsules has been co-administered with a variety of medications (e.g., cytotoxic agents,
280 anti-infective agents, sedatives, or opioid analgesics) without resulting in any clinically
281 significant drug/drug interactions. Although no drug/drug interactions were discovered
282 during the clinical trials of MARINOL Capsules, cannabinoids may interact with other
283 medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is
284 highly protein bound to plasma proteins, and therefore, might displace other protein-
285 bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners

286 should monitor patients for a change in dosage requirements when administering
 287 dronabinol to patients receiving other highly protein-bound drugs. Published reports of
 288 drug/drug interactions involving cannabinoids are summarized in the following table.
 289

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
Antipyrine, 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

290
 291 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies
 292 in mice and rats have been conducted under the US National Toxicology Program (NTP).
 293 In the 2-year carcinogenicity study in rats, there was no evidence of carcinogenicity at
 294 doses up to 50 mg/kg/day, about 20 times the maximum recommended human dose on a
 295 body surface area basis. In the 2-year carcinogenicity study in mice, treatment with
 296 dronabinol at 125 mg/kg/day, about 25 times the maximum recommended human dose on
 297 a body surface area basis, produced thyroid follicular cell adenoma in both male and
 298 female mice but not at 250 or 500 mg/kg/day.

299
 300 Dronabinol was not genotoxic in the Ames tests, the *in vitro* chromosomal aberration
 301 test in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. It, however,
 302 produced a weak positive response in a sister chromatid exchange test in Chinese hamster
 303 ovary cells.

304
 305 In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30
 306 to 150 mg/m², equivalent to 0.3 to 1.5 times maximum recommended human dose

307 (MRHD) of 90 mg/m²/day in cancer patients or 2 to 10 times MRHD of 15 mg/m²/day in
308 AIDS patients, reduced ventral prostate, seminal vesicle and epididymal weights and
309 caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of
310 developing germ cells, and number of Leydig cells in the testis were also observed.
311 However, sperm count, mating success and testosterone levels were not affected. The
312 significance of these animal findings in humans is not known.

313

314 **Pregnancy:** Pregnancy Category C. Reproduction studies with dronabinol have been
315 performed in mice at 15 to 450 mg/m², equivalent to 0.2 to 5 times maximum
316 recommended human dose (MRHD) of 90 mg/m²/day in cancer patients or 1 to 30 times
317 MRHD of 15 mg/m²/day in AIDS patients, and in rats at 74 to 295 mg/m² (equivalent to
318 0.8 to 3 times MRHD of 90 mg/m² in cancer patients or 5 to 20 times MRHD of 15
319 mg/m²/day in AIDS patients). These studies have revealed no evidence of teratogenicity
320 due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal
321 weight gain and number of viable pups and increased fetal mortality and early
322 resorptions. Such effects were dose dependent and less apparent at lower doses which
323 produced less maternal toxicity. There are no adequate and well-controlled studies in
324 pregnant women. Dronabinol should be used only if the potential benefit justifies the
325 potential risk to the fetus.

326

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

330

331 **Geriatric Use:** Clinical studies of MARINOL Capsules in AIDS and cancer patients
332 did not include the sufficient numbers of subjects aged 65 and over to determine whether
333 they respond differently from younger subjects. Other reported clinical experience has
334 not identified differences in responses between the elderly and younger patients. In
335 general, dose selection for an elderly patient should be cautious usually starting at the low
336 end of the dosing range, reflecting the greater frequency of falls, decreased hepatic, renal,
337 or cardiac function, increased sensitivity to psychoactive effects and of concomitant
338 disease or other drug therapy.

339

340 **ADVERSE REACTIONS**

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

348

349 A cannabinoid dose-related “high” (easy laughing, elation and heightened awareness)
350 has been reported by patients receiving MARINOL Capsules in both the antiemetic
351 (24%) and the lower dose appetite stimulant clinical trials (8%). (See **Clinical Trials.**)

352

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

358

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

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

363 *Body as a whole:* Asthenia.

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

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

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

369 *Incidence of events 3% to 10%

370

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

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

374 *Cardiovascular:* Conjunctivitis*, hypotension*.

375 *Digestive:* Diarrhea*, fecal incontinence.

376 *Musculoskeletal:* Myalgias.

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

378 *Skin and Appendages:* Flushing*.

379 *Special senses:* Vision difficulties.

380 *Incidence of events 0.3% to 1%

381

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

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

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

386 *Digestive:* Anorexia, hepatic enzyme elevation.

387 *Respiratory:* Cough, rhinitis, sinusitis.

388 *Skin and Appendages:* Sweating.

389

390 **Postmarketing Experience**

391 Seizure and seizure-like activity have been reported in patients receiving MARINOL
 392 Capsules during marketed use of the drug and in clinical trials. (See **PRECAUTIONS**
 393 and **OVERDOSAGE**.) **Reports of fatigue have also been received.** A causal
 394 relationship between MARINOL Capsules and these events has not been established.

395

396 **DRUG ABUSE AND DEPENDENCE**

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

402

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

408

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

413

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

420

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

426

427 **OVERDOSAGE**

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

436

437 The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/
438 70 kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg
439 (28 mg/70 kg) of MARINOL Capsules.

440

441 **Management:** A potentially serious oral ingestion, if recent, should be managed with
442 gut decontamination. In unconscious patients with a secure airway, instill activated

443 charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline
444 cathartic or sorbitol may be added to the first dose of activated charcoal. Patients
445 experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet
446 area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *po*) may be used for
447 treatment of extreme agitation. Hypotension usually responds to Trendelenburg position
448 and IV fluids. Pressors are rarely required.

449

450 **DOSAGE AND ADMINISTRATION**

451 **Appetite Stimulation:** Initially, 2.5 mg MARINOL Capsules should be administered
452 orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this
453 5 mg/day dosage of MARINOL Capsules, the dosage can be reduced to 2.5 mg/day,
454 administered as a single dose in the evening or at bedtime. If clinically indicated and in
455 the absence of significant adverse effects, the dosage may be gradually increased to a
456 maximum of 20 mg/day MARINOL Capsules, administered in divided oral doses.
457 Caution should be exercised in escalating the dosage of MARINOL Capsules because of
458 the increased frequency of dose-related adverse experiences at higher dosages. (See

459 **PRECAUTIONS.**)

460

461 **Antiemetic:** MARINOL Capsules is best administered at an initial dose of 5 mg/m²,
462 given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours
463 after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m² dose
464 prove to be ineffective, and in the absence of significant side effects, the dose may be
465 escalated by 2.5 mg/m² increments to a maximum of 15 mg/m² per dose. Caution should
466 be exercised in dose escalation, however, as the incidence of disturbing psychiatric
467 symptoms increases significantly at maximum dose. (See **PRECAUTIONS.**)

468

469 **Storage Conditions**

470 **MARINOL Capsules should be packaged in a well-closed container and stored in a**
471 **cool environment between 8° and 15°C (46° and 59°F) and alternatively could be**
472 **stored in a refrigerator. Protect from freezing.**

473

474 **HOW SUPPLIED**

475 **MARINOL Capsules (dronabinol solution in sesame oil in soft gelatin capsules)**

476

477 **2.5 mg white capsules (Identified UM).**

478 NDC 0051-0021-21 (Bottle of 60 capsules).

479

480 **5 mg dark brown capsules (Identified UM).**

481 NDC 0051-0022-21 (Bottle of 60 capsules).

482

483 **10 mg orange capsules (Identified UM).**

484 NDC 0051-0023-21 (Bottle of 60 capsules).

485

486 MARINOL is a registered trademark of Unimed Pharmaceuticals, Inc. and is

487 Manufactured by Banner Pharmacaps, Inc.

488 High Point, NC 27265

489
490 For:
491 Unimed Pharmaceuticals, Inc.
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