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Rx only

MARINOL®  
(dronabinol) Capsules

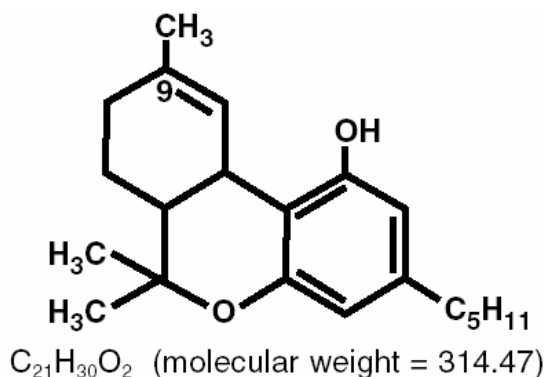
BAR CODE

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## 1 DESCRIPTION

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



5  
6 Dronabinol, the active ingredient in MARINOL® (dronabinol) Capsules, is synthetic  
7 delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a  
8 naturally occurring component of *Cannabis sativa L.* (Marijuana).  
9

10 Dronabinol is a light yellow resinous oil that is sticky at room temperature and  
11 hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame  
12 oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.  
13

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

## 22 CLINICAL PHARMACOLOGY

23 Dronabinol is an orally active cannabinoid which, like other cannabinoids, has complex  
24 effects on the central nervous system (CNS), including central sympathomimetic activity.  
25 Cannabinoid receptors have been discovered in neural tissues. These receptors may play  
26 a role in mediating the effects of dronabinol and other cannabinoids.  
27

## 28 **Pharmacodynamics**

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

32  
33 Dronabinol also demonstrates reversible effects on appetite, mood, cognition,  
34 memory, and perception. These phenomena appear to be dose-related, increasing in  
35 frequency with higher dosages, and subject to great interpatient variability.

36  
37 After oral administration, dronabinol has an onset of action of approximately 0.5 to 1  
38 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6  
39 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer  
40 after administration.

41  
42 Tachyphylaxis and tolerance develop to some of the pharmacologic effects of  
43 dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on  
44 sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol  
45 exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol,  
46 administered orally in divided doses, for 16 days. An initial tachycardia induced by  
47 dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A  
48 decrease in supine blood pressure, made worse by standing, was also observed initially.  
49 These volunteers developed tolerance to the cardiovascular and subjective adverse CNS  
50 effects of dronabinol within 12 days of treatment initiation.

51  
52 Tachyphylaxis and tolerance do not, however, appear to develop to the appetite  
53 stimulant effect of MARINOL Capsules. In studies involving patients with Acquired  
54 Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of MARINOL  
55 Capsules has been sustained for up to five months in clinical trials, at dosages ranging  
56 from 2.5 mg/day to 20 mg/day.

## 57 58 **Pharmacokinetics**

59 **Absorption and Distribution:** MARINOL Capsules is almost completely absorbed  
60 (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic  
61 metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the  
62 systemic circulation. Dronabinol has a large apparent volume of distribution,  
63 approximately 10 L/kg, because of its lipid solubility. The plasma protein binding of  
64 dronabinol and its metabolites is approximately 97%.

65  
66 The elimination phase of dronabinol can be described using a two compartment  
67 model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25  
68 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites  
69 may be excreted at low levels for prolonged periods of time.

70  
71 The pharmacokinetics of dronabinol after single doses (2.5, 5, and 10 mg) and  
72 multiple doses (2.5, 5, and 10 mg given twice a day; BID) have been studied in healthy  
73 women and men.

74  
75 **Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol**  
76 **in Healthy Volunteers (n=34; 20-45 years) under Fasted Conditions**  
77

Mean (SD) PK Parameter Values			
BID Dose	C <sub>max</sub> ng/mL	Median T <sub>max</sub> (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)

78  
79 A slight increase in dose proportionality on mean C<sub>max</sub> and AUC(0-12) of  
80 dronabinol was observed with increasing dose over the dose range studied.

81  
82 **Metabolism:** Dronabinol undergoes extensive first-pass hepatic metabolism, primarily  
83 by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol  
84 and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately  
85 equal concentrations in plasma. Concentrations of both parent drug and metabolite peak  
86 at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values  
87 for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of  
88 cannabinoid distribution.

89  
90 **Elimination:** Dronabinol and its biotransformation products are excreted in both feces  
91 and urine. Biliary excretion is the major route of elimination with about half of a radio-  
92 labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to  
93 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the  
94 feces.

95  
96 Following single dose administration, low levels of dronabinol metabolites have been  
97 detected for more than 5 weeks in the urine and feces.

98  
99 In a study of MARINOL Capsules involving AIDS patients, urinary  
100 cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week  
101 period. The urinary cannabinoid/creatinine ratio was closely correlated with dose. No  
102 increase in the cannabinoid/creatinine ratio was observed after the first two weeks of  
103 treatment, indicating that steady-state cannabinoid levels had been reached. This  
104 conclusion is consistent with predictions based on the observed terminal half-life of  
105 dronabinol.

106  
107 **Special Populations:** The pharmacokinetic profile of MARINOL Capsules has not  
108 been investigated in either pediatric or geriatric patients.

109  
110 **Clinical Trials**

111 **Appetite Stimulation:** The appetite stimulant effect of MARINOL Capsules in the  
112 treatment of AIDS-related anorexia associated with weight loss was studied in a  
113 randomized, double-blind, placebo-controlled study involving 139 patients. The initial

114 dosage of MARINOL Capsules in all patients was 5 mg/day, administered in doses of 2.5  
 115 mg one hour before lunch and one hour before supper. In pilot studies, early morning  
 116 administration of MARINOL Capsules appeared to have been associated with an  
 117 increased frequency of adverse experiences, as compared to dosing later in the day. The  
 118 effect of MARINOL Capsules on appetite, weight, mood, and nausea was measured at  
 119 scheduled intervals during the six-week treatment period. Side effects (feeling high,  
 120 dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage  
 121 level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper  
 122 or bedtime.

123

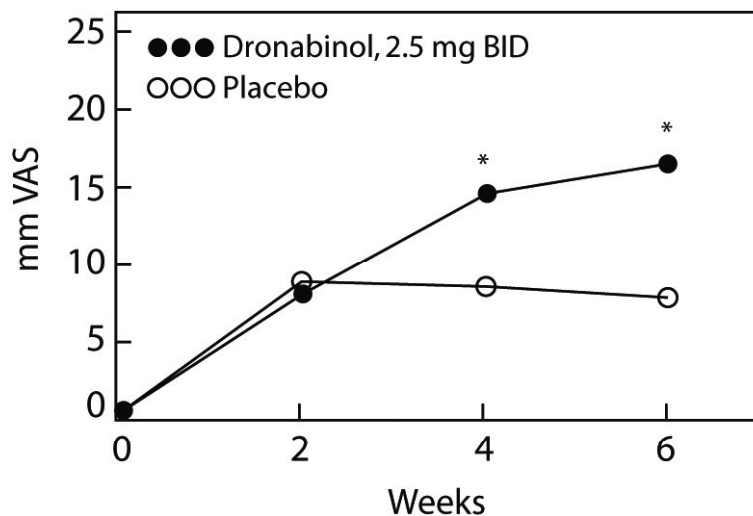
124 Of the 112 patients that completed at least 2 visits in the randomized, double-blind,  
 125 placebo-controlled study, 99 patients had appetite data at 4-weeks (50 received  
 126 MARINOL and 49 received placebo) and 91 patients had appetite data at 6-weeks (46  
 127 received MARINOL and 45 received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

131

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

135

### Mean Appetite Change from Baseline



\*p-value<0.05

136

137

138

139 **Antiemetic:** MARINOL Capsules treatment of chemotherapy-induced emesis was  
 140 evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of  
 141 various malignancies. The antiemetic efficacy of MARINOL Capsules was greatest in

142 patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's  
 143 lymphomas. MARINOL Capsules dosages ranged from 2.5 mg/day to 40 mg/day,  
 144 administered in equally divided doses every four to six hours (four times daily). As  
 145 indicated in the following table, escalating the MARINOL Capsules dose above 7 mg/m<sup>2</sup>  
 146 increased the frequency of adverse experiences, with no additional antiemetic benefit.

147  
 148 **MARINOL Capsules Dose: Response Frequency and Adverse Experiences\***  
 149 (N = 750 treatment courses)

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

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

151

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

155

#### 156 **INDIVIDUALIZATION OF DOSAGES**

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

160

161 ***Appetite Stimulation:*** In the clinical trials, the majority of patients were treated with  
 162 5 mg/day MARINOL Capsules, although the dosages ranged from 2.5 to 20 mg/day. For  
 163 an adult:

- 164 1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling  
 165 high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days  
 166 with continued dosage.
- 167
- 168 2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If  
 169 symptoms continue to be a problem, taking the single dose in the evening or at  
 170 bedtime may reduce their severity.
- 171
- 172 3. When adverse effects are absent or minimal and further therapeutic effect is desired,  
 173 increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg.  
 174 Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been  
 175 tolerated in about half of the patients in appetite stimulation studies.

176

177 The pharmacologic effects of MARINOL Capsules are reversible upon treatment  
 178 cessation.

179

180 ***Antiemetic:*** Most patients respond to 5 mg three or four times daily. Dosage may be  
 181 escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results.

182 Therapy should be initiated at the lowest recommended dosage and titrated to clinical  
183 response. Administration of MARINOL Capsules with phenothiazines, such as  
184 prochlorperazine, has resulted in improved efficacy as compared to either drug alone,  
185 without additional toxicity.

186

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

192

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

197

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

204

## 205 **INDICATIONS AND USAGE**

206 MARINOL Capsules is indicated for the treatment of:

207

208

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

211

## 212 **CONTRAINDICATIONS**

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

216

## 217 **WARNINGS**

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

221

## 222 **PRECAUTIONS**

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

226

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

235 MARINOL Capsules should be used with caution in patients with cardiac disorders  
236 because of occasional hypotension, possible hypertension, syncope, or tachycardia. (See  
237 **CLINICAL PHARMACOLOGY**.)  
238

239 MARINOL Capsules should be used with caution in patients with a history of  
240 substance abuse, including alcohol abuse or dependence, because they may be more  
241 prone to abuse MARINOL Capsules as well. Multiple substance abuse is common and  
242 marijuana, which contains the same active compound, is a frequently abused substance.  
243

244 MARINOL Capsules should be used with caution and careful psychiatric monitoring  
245 in patients with mania, depression, or schizophrenia because MARINOL Capsules may  
246 exacerbate these illnesses.  
247

248 MARINOL Capsules should be used with caution in patients receiving concomitant  
249 therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for  
250 additive or synergistic CNS effects.  
251

252 MARINOL Capsules should be used with caution in elderly patients because they  
253 may be more sensitive to the neurological, psychoactive, and postural hypotensive effects  
254 of the drug. (See **INDIVIDUALIZATION OF DOSAGES**.)  
255

256 MARINOL Capsules should be used with caution in pregnant patients, nursing  
257 mothers, or pediatric patients because it has not been studied in these patient populations.  
258

259 **Information for Patients:** Patients receiving treatment with MARINOL Capsules  
260 should be alerted to the potential for additive central nervous system depression if  
261 MARINOL Capsules is used concomitantly with alcohol or other CNS depressants such  
262 as benzodiazepines and barbiturates.  
263

264 Patients receiving treatment with MARINOL Capsules should be specifically warned  
265 not to drive, operate machinery, or engage in any hazardous activity until it is established  
266 that they are able to tolerate the drug and to perform such tasks safely.  
267

268 Patients using MARINOL Capsules should be advised of possible changes in mood  
269 and other adverse behavioral effects of the drug so as to avoid panic in the event of such  
270 manifestations. Patients should remain under the supervision of a responsible adult during  
271 initial use of MARINOL Capsules and following dosage adjustments.  
272

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

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

285  
 286 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies  
 287 in mice and rats have been conducted under the US National Toxicology Program (NTP).  
 288 In the 2-year carcinogenicity study in rats, there was no evidence of carcinogenicity at  
 289 doses up to 50 mg/kg/day, about 20 times the maximum recommended human dose on a  
 290 body surface area basis. In the 2-year carcinogenicity study in mice, treatment with  
 291 dronabinol at 125 mg/kg/day, about 25 times the maximum recommended human dose on  
 292 a body surface area basis, produced thyroid follicular cell adenoma in both male and  
 293 female mice but not at 250 or 500 mg/kg/day.

294

295 Dronabinol was not genotoxic in the Ames tests, the *in vitro* chromosomal aberration  
296 test in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. It, however,  
297 produced a weak positive response in a sister chromatid exchange test in Chinese hamster  
298 ovary cells.

299

300 In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30  
301 to 150 mg/m<sup>2</sup>, equivalent to 0.3 to 1.5 times maximum recommended human dose  
302 (MRHD) of 90 mg/m<sup>2</sup>/day in cancer patients or 2 to 10 times MRHD of 15 mg/m<sup>2</sup>/day in  
303 AIDS patients, reduced ventral prostate, seminal vesicle and epididymal weights and  
304 caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of  
305 developing germ cells, and number of Leydig cells in the testis were also observed.  
306 However, sperm count, mating success and testosterone levels were not affected. The  
307 significance of these animal findings in humans is not known.

308

309 **Pregnancy:** Pregnancy Category C. Reproduction studies with dronabinol have been  
310 performed in mice at 15 to 450 mg/m<sup>2</sup>, equivalent to 0.2 to 5 times maximum  
311 recommended human dose (MRHD) of 90 mg/m<sup>2</sup>/day in cancer patients or 1 to 30 times  
312 MRHD of 15 mg/m<sup>2</sup>/day in AIDS patients, and in rats at 74 to 295 mg/m<sup>2</sup> (equivalent to  
313 0.8 to 3 times MRHD of 90 mg/m<sup>2</sup> in cancer patients or 5 to 20 times MRHD of 15  
314 mg/m<sup>2</sup>/day in AIDS patients). These studies have revealed no evidence of teratogenicity  
315 due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal  
316 weight gain and number of viable pups and increased fetal mortality and early  
317 resorptions. Such effects were dose dependent and less apparent at lower doses which  
318 produced less maternal toxicity. There are no adequate and well-controlled studies in  
319 pregnant women. Dronabinol should be used only if the potential benefit justifies the  
320 potential risk to the fetus.

321

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

325

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

334

### 335 **ADVERSE REACTIONS**

336 Adverse experiences information summarized in the tables below was derived from well-  
337 controlled clinical trials conducted in the US and US territories involving 474 patients  
338 exposed to MARINOL Capsules. Studies of AIDS-related weight loss included 157  
339 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo.

340 Studies of different durations were combined by considering the first occurrence of  
 341 events during the first 28 days. Studies of nausea and vomiting related to cancer  
 342 chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo.  
 343

344 A cannabinoid dose-related “high” (easy laughing, elation and heightened awareness)  
 345 has been reported by patients receiving MARINOL Capsules in both the antiemetic  
 346 (24%) and the lower dose appetite stimulant clinical trials (8%). (See **Clinical Trials.**)  
 347

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

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

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

---

358 *Body as a whole:* Asthenia.

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

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

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

---

364 \*Incidence of events 3% to 10%

365

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

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

---

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

370 *Digestive:* Diarrhea\*, fecal incontinence.

371 *Musculoskeletal:* Myalgias.

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

373 *Skin and Appendages:* Flushing\*.

374 *Special senses:* Vision difficulties.

---

375 \*Incidence of events 0.3% to 1%

376

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

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

---

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

381 *Digestive:* Anorexia, hepatic enzyme elevation.

382 *Respiratory:* Cough, rhinitis, sinusitis.

383 *Skin and Appendages:* Sweating.

---

384

**385 Postmarketing Experience**

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

390

**391 DRUG ABUSE AND DEPENDENCE**

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

397

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

403

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

408

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

415

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

421

**422 OVERDOSAGE**

423 Signs and symptoms following MILD MARINOL Capsules intoxication include  
424 drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened  
425 conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include  
426 memory impairment, depersonalization, mood alteration, urinary retention, and reduced  
427 bowel motility; and following SEVERE intoxication include decreased motor  
428 coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients

429 may experience panic reactions and seizures may occur in patients with existing seizure  
430 disorders.

431

432 The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/  
433 70 kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg  
434 (28 mg/70 kg) of MARINOL Capsules.

435

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

444

#### 445 **DOSAGE AND ADMINISTRATION**

446 **Appetite Stimulation:** Initially, 2.5 mg MARINOL Capsules should be administered  
447 orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this  
448 5 mg/day dosage of MARINOL Capsules, the dosage can be reduced to 2.5 mg/day,  
449 administered as a single dose in the evening or at bedtime. If clinically indicated and in  
450 the absence of significant adverse effects, the dosage may be gradually increased to a  
451 maximum of 20 mg/day MARINOL Capsules, administered in divided oral doses.  
452 Caution should be exercised in escalating the dosage of MARINOL Capsules because of  
453 the increased frequency of dose-related adverse experiences at higher dosages. (See  
454 **PRECAUTIONS.**)

455

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

463

#### 464 **Storage Conditions**

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

468

#### 469 **HOW SUPPLIED**

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

471

472 **2.5 mg white capsules (Identified UM).**

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

474

475 **5 mg dark brown capsules (Identified UM).**  
476 NDC 0051-0022-21 (Bottle of 60 capsules).

477

478 **10 mg orange capsules (Identified UM).**  
479 NDC 0051-0023-21 (Bottle of 60 capsules).

480

481 **Manufactured by:**

482 Banner Pharmacaps, Inc.

483 High Point, NC 27265

484

485 For:

486 Solvay Pharmaceuticals, Inc.

487 Marietta, GA 30062

488

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