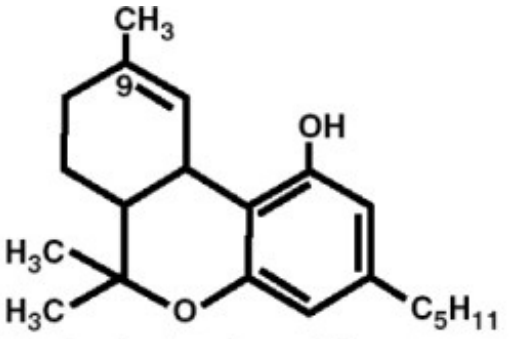
MARINOL- dronabinol capsule
AbbVie Inc.

MARINOL®
(dronabinol capsules, USP)

Rx only
CIII

DESCRIPTION

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



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

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

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

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

CLINICAL PHARMACOLOGY

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

Pharmacodynamics

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

hypotension and/or syncope upon abrupt standing.

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

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

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

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

Pharmacokinetics

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

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

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

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

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)

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.

Metabolism: Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 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.

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

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

In a study of MARINOL 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.

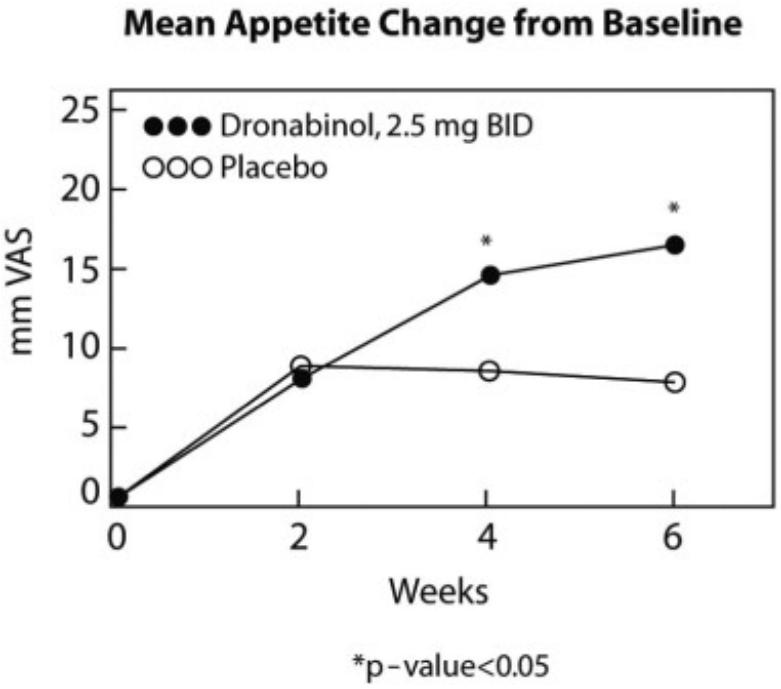
Special Populations: The pharmacokinetic profile of MARINOL capsules has not been investigated in either pediatric or geriatric patients.

Clinical Trials

Appetite Stimulation: The appetite stimulant effect of MARINOL capsules 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 capsules 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 capsules appeared to have been associated with an increased frequency of adverse experiences, as compared to dosing later in the day. The effect of MARINOL capsules 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.

Of the 112 patients that completed at least 2 visits in the randomized, double-blind, placebo-controlled study, 99 patients had appetite data at 4-weeks (50 received MARINOL and 49 received placebo) and 91 patients had appetite data at 6-weeks (46 received MARINOL and 45 received placebo). A statistically significant difference between MARINOL capsules and placebo was seen in appetite as measured by the visual analog scale at weeks 4 and 6 (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 capsules in an open-label study, in which there was a sustained improvement in appetite.



Antiemetic: MARINOL capsules 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 capsules was greatest in patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's lymphomas. MARINOL capsules dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). As indicated in the following table, escalating the MARINOL capsules dose above 7 mg/m^2 increased the frequency of adverse experiences, with no additional antiemetic benefit.

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

*Nondysphoric events consisted of drowsiness, tachycardia, etc.

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

INDIVIDUALIZATION OF DOSAGES

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

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

1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days with continued dosage.
2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If symptoms

continue to be a problem, taking the single dose in the evening or at bedtime may reduce their severity.
3. When adverse effects are absent or minimal and further therapeutic effect is desired, increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies.

The pharmacologic effects of MARINOL capsules are reversible upon treatment cessation.

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

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

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

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

INDICATIONS AND USAGE

MARINOL capsules is indicated for the treatment of:
1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General: The risk/benefit ratio of MARINOL capsules use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the

effects of MARINOL capsules.

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

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

MARINOL capsules 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 capsules as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance.

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

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

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

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

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

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

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

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

CONCOMITANT DRUG	CLINICAL EFFECT(S)
Amphetamines, cocaine, other sympathomimetic	Additive hypertension, tachycardia, possibly

agents	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

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

Dronabinol 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.

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

Pregnancy: Pregnancy Category C. Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m^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 dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Dronabinol should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Use of MARINOL capsules is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human

breast milk and is absorbed by the nursing baby.

Geriatric Use: Clinical studies of MARINOL capsules 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 falls, decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

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

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

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

PROBABLY CAUSALLY RELATED: Incidence greater than 1%.

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

Body as a whole: Asthenia.
Cardiovascular: Palpitations, tachycardia, vasodilation/facial flush.
Digestive: Abdominal pain*, nausea*, vomiting*.
Nervous system: (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness*, euphoria*, (hallucination), paranoid reaction*, somnolence*, thinking abnormal*.

*Incidence of events 3% to 10%

PROBABLY CAUSALLY RELATED: Incidence less than 1%.

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

Cardiovascular: Hypotension*.
Digestive: Diarrhea*, fecal incontinence.
Musculoskeletal: Myalgias.
Nervous system: Depression, nightmares, speech difficulties, tinnitus.
Skin and Appendages: Flushing*.
Special senses: Conjunctivitis*, vision difficulties.

*Incidence of events 0.3% to 1%

CAUSAL RELATIONSHIP UNKNOWN: Incidence less than 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 and Appendages: Sweating.

Postmarketing Experience

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

DRUG ABUSE AND DEPENDENCE

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

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

In an open-label study in patients with AIDS who received MARINOL capsules 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.

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

Antiemetic: MARINOL capsules 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. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose. (See **PRECAUTIONS.**)

Storage Conditions

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

HOW SUPPLIED

MARINOL® (dronabinol capsules, USP)

2.5 mg white capsules (Identified UM).
NDC 0051-0021-21 (Bottle of 60 capsules).

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

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

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.

1248A00 06/16 June, 2016

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PATIENT INFORMATION

MARINOL® (dronabinol capsules, USP)
2.5 mg, 5 mg, 10 mg
for use in the loss of appetite
associated with weight loss
in patients with AIDS.

IMPORTANT

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

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

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

INTRODUCTION

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

MARINOL capsules contains man-made dronabinol (THC). Dronabinol also occurs naturally, and has been extracted from *Cannabis sativa L*. (marijuana).

PRECAUTIONS

Be sure to tell your doctor if you:

- have or had heart disease
- have or had cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia
- have current or a history of drug abuse
- have current or a history of alcohol abuse
- have or had mental health problems (mania, depression, schizophrenia)
- have a history of seizure disorder and/or seizure-like activity
- have allergies to drugs
- are pregnant or nursing, or become pregnant

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

MARINOL capsules should be used with caution in children because it has not been studied in children.

MARINOL capsules should be used with caution in elderly patients because they may be more sensitive to the neurological, psychoactive, and postural hypotensive effects of the drug.

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

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

You may experience changes in mood or have other effects when first taking MARINOL capsules. Be sure that there is a responsible person nearby when you first take MARINOL capsules or when there is an adjustment in your dose.

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

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

INFORMATION ABOUT USING MARINOL CAPSULES

Introduction

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

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

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

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

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

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

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

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

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

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

How to Eat

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

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

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

Blend one cup of nonfat dry milk powder with one quart of whole milk. Refrigerate and use "double strength" milk for all traditional uses (puddings, cereal, shakes, soups).

Foods with a softer consistency, such as applesauce, may aid swallowing. Creamed sauces or gravies also moisten food to encourage swallowing.

Creating an appetizing meal involves more than just food. Try to eat in a pleasant atmosphere – sit in a comfortable chair, use a tablecloth and china, invite a friend to share your meal.

What to Eat
Planning ahead is one of the most effective ways to deal with a loss of appetite. Stock up on staple foods, particularly those high in calories and protein, so they're available when you need them. Include favorite foods on your shopping list. Also consider these protein and nutrient dense foods:

- Nonfat dry milk powder
- Powdered breakfast drinks
- Peanut butter and jelly
- Pudding cups
- "Trail mix" (dried fruit, nuts, cereals)
- Creamed soups
- Canned (or frozen) fruit in heavy syrup
- Canned tuna, chicken or other sandwich spreads
- Boxed macaroni and cheese

In addition to staples, refrigerated and frozen foods contribute important nutrients to an adequate diet. Several key choices, high in protein and calories, are listed below:

- Yogurt
- Cheeses
- Cold cuts, beef and poultry
- Cottage cheese
- Ice cream and sherbet
- Popsicles or pudding pops
- Hard cooked eggs or pasteurized eggs*

*Raw or undercooked cracked eggs pose danger of *Salmonella*. The compromised immune function of persons with AIDS places them at greater than average risk from *Salmonella* infection.

Commercial food supplements are also available to boost your caloric and nutrient intake. Offered in a variety of flavors and textures, these products supply a concentrated source of calories and protein. You may want to ask your treatment provider for more information about supplements. You may also request a referral to a registered dietitian who can provide individualized dietary recommendations to you.

When to Eat
"Nutritious" meals can be eaten three times a day, but frequent, small snacks or meals can help you consume the calories and protein you need without feeling full from a large meal. Eat when you feel hungry, using modern technology, including your microwave, to quickly prepare a nutritious snack or meal.

Storage Instructions
The best place to store MARINOL capsules is in a cool place (46-59°F; 8-15°C) or in the refrigerator. Be careful that the capsules don't freeze. Heat or moisture may cause your MARINOL capsules to break down or stick together, so keep your medicine away from heat and direct light, and potentially damp places like in the bathroom or near the kitchen sink.

If You Are Taking Medicines
MARINOL capsules use may change the effect of other medicines. It is important to tell your doctor about all the medicines you are taking including all non-prescription medication.

What to Watch For (Adverse Effects)

You should not smoke marijuana while using MARINOL capsules. It is possible to get too much dronabinol (an overdose), especially if you use MARINOL capsules and smoke marijuana at the same time. 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 Have Problems in the First Few Days
When you first use MARINOL capsules 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 CAPSULES AND CALL YOUR DOCTOR AT ONCE.

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.

1248A00-P 06/16 June, 2016

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NDC 0051-0021-21

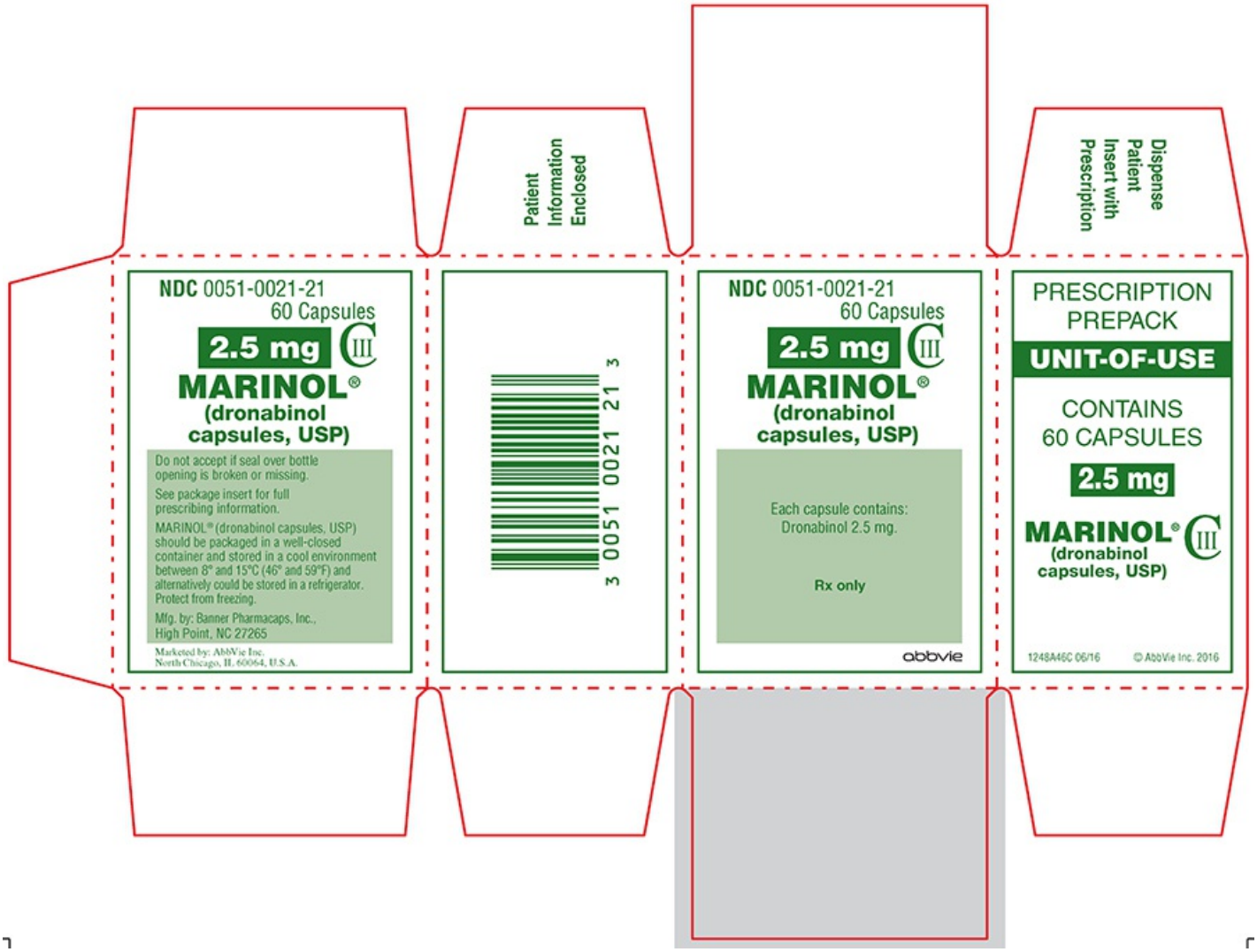
60 Capsules

2.5 mg CIII

MARINOL® (dronabinol capsules, USP)

Each capsule contains: Dronabinol 2.5 mg.

Rx only abbvie



NDC 0051-0022-21

60 Capsules

5 mg CIII

MARINOL® (dronabinol capsules, USP)

Each capsule contains: Dronabinol 5 mg.

Rx only abbvie

NDC 0051-0023-21

60 Capsules

10 mg

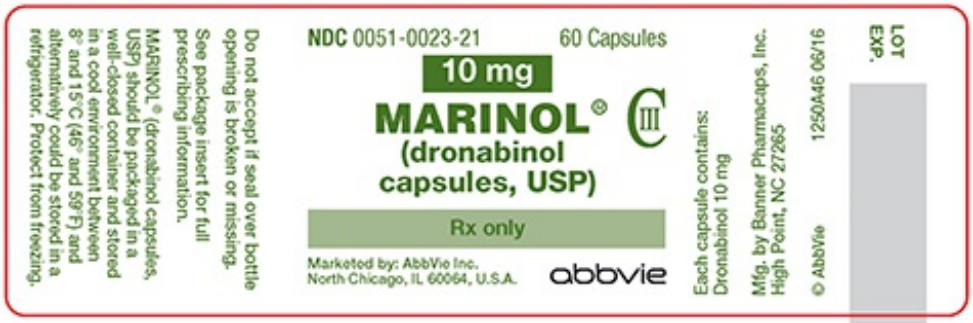
MARINOL® CIII (dronabinol capsules, USP)

Each capsule contains: Dronabinol 10 mg.

Rx only

Marketed by: AbbVie Inc.
North Chicago, IL 60064, U.S.A.

abbvie



MARINOL

dronabinol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-0021
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
dronabinol (UNII: 7J8897W37S) (dronabinol - UNII:7J8897W37S)	dronabinol	2.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
glycerin (UNII: PDC6A3C0OX)	
sesame oil (UNII: QX10HYY4QV)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE (white)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	8mm
Flavor		**Imprint Code**	UM
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0051-0021-21	1 in 1 CARTON	07/13/2010	
1		60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018651	07/13/2010	

MARINOL

dronabinol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-0022
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
dronabinol (UNII: 7J8897W37S) (dronabinol - UNII:7J8897W37S)	dronabinol	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
FERRIC OXIDE RED (UNII: 1K09F3G675)	
ferrosoferric oxide (UNII: XM0M87F357)	
glycerin (UNII: PDC6A3C0OX)	
sesame oil (UNII: QX10HYY4QV)	
titanium dioxide (UNII: 15FIX9V2JP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	

Product Characteristics			
Color	BROWN (brown)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	8mm
Flavor		**Imprint Code**	UM
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0051-0022-21	1 in 1 CARTON	07/13/2010	
1		60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018651	07/13/2010	

MARINOL

dronabinol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-0023
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
dronabinol (UNII: 7J8897W37S) (dronabinol - UNII:7J8897W37S)	dronabinol	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
FERRIC OXIDE RED (UNII: 1K09F3G675)	
ferric oxide yellow (UNII: EX438O2MRT)	
glycerin (UNII: PDC6A3C0OX)	
sesame oil (UNII: QX10HYY4QV)	
titanium dioxide (UNII: 15FIX9V2JP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	

Product Characteristics			
Color	ORANGE (orange)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	8mm
Flavor		**Imprint Code**	UM
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0051-0023-21	1 in 1 CARTON	07/13/2010	
1		60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018651	07/13/2010	

Labeler - AbbVie Inc. (078458370)

Revised: 12/2016 AbbVie Inc.