

PRODUCT MONOGRAPH

N CESAMET[®]

Nabilone

Capsules; 1mg, 0.5 mg, 0.25 mg

Antiemetic

Valeant Canada limitée/Limited
4787 Levy Street,
Montreal, Quebec H4R 2P9

Date of Revision:
March 17, 2009

Submission Control No: 124406

NAME OF DRUG

^NCESAMET[®] capsules

(nabilone)

THERAPEUTIC CLASSIFICATION

Antiemetic Agent

ACTION

^NCESAMET[®] (nabilone) is a synthetic cannabinoid with antiemetic properties which have been found to be of value in the management of some patients with nausea and vomiting associated with cancer chemotherapy. It also has sedative and psychotropic effects.

After oral administration, comparable peak plasma levels of nabilone and of its carbinol metabolite were attained within 2 hours. The combined plasma concentrations of nabilone and of its carbinol metabolite accounted for, at most, 10 to 20% of the total radiocarbon concentration in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the total radiocarbon was of the order of 35 hours.

Of the two major possible metabolic pathways, stereo-specific enzymatic reduction and direct enzymatic oxidation, the latter appears to be the more important in man.

The drug and its metabolites are eliminated mainly in the feces (approximately 65%) and to a lesser extent in the urine (approximately 20%). The major excretory pathway is the biliary system.

INDICATIONS

Adults: > 18 years

^NCESAMET[®] (nabilone) is indicated for the management of severe nausea and vomiting associated with cancer chemotherapy.

Pediatrics: < 18 years

The safety and efficacy of ^NCESAMET[®] in the pediatric population have not been established and its use is not recommended in this patient population.

Geriatrics: > 65 years

^NCESAMET[®] should be used with caution in the elderly. (See PRECAUTIONS).

CONTRAINDICATIONS

^NCESAMET[®] (nabilone) is contraindicated in patients with known sensitivity to marijuana or other cannabinoid agents, and in those with a history of psychotic reactions.

WARNINGS

^NCESAMET[®] (nabilone) should be used with extreme caution in patients with severe liver dysfunction and in those with a history of non-psychotic emotional disorders.

^NCESAMET[®] should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances.

^NCESAMET[®] should not be used during pregnancy, in nursing mothers, or pediatric patients since its safety under these conditions has not been established.

PRECAUTIONS

Since ^NCESAMET[®] (nabilone) will often impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car and operating machinery, the patient should be warned accordingly and should not be permitted to drive or engage in dangerous tasks until the effects of nabilone are no longer present.

Adverse psychotropic reactions can persist for 48 to 72 hours following cessation of treatment.

Since ^NCESAMET[®] elevates supine and standing heart rates and causes postural hypotension, it should be used with caution in the elderly and in patients with hypertension or heart disease.

Drug Interactions: Potential interactions between ^NCESAMET[®], and diazepam; sodium secobarbital; alcohol; or codeine, were evaluated. The depressant effects of the combinations were additive. Psychomotor function was particularly impaired with concurrent use of diazepam.

Pediatric Use: The safety and efficacy in children under the age of 18 has not been established. Therefore the use of ^NCESAMET[®] in this patient population is not recommended.

ADVERSE REACTIONS

The most frequently observed adverse reactions to nabilone and their incidences reported in the course of clinical trials were as follows: drowsiness (66.0%), vertigo (58.8%), psychological high (38.8%), dry mouth (21.6%), depression (14.0%), ataxia (12.8%), blurred vision (12.8%), sensation disturbance (12.4%), anorexia (7.6%), asthenia (7.6%), headache (7.2%), orthostatic hypotension (5.2%), euphoria (4.0%) and hallucinations (2.0%).

The following adverse reactions were observed in less than 1% of the patients who were administered nabilone in the course of the clinical trials: tachycardia, tremors, syncope,

nightmares, distortion in the perception of time, confusion, dissociation, dysphoria, psychotic reactions and seizures.

Spontaneously Reported Adverse Reactions: The following adverse reactions listed in order of decreasing frequency by body system have been reported since ^NCESAMET[®] has been marketed. All events are listed regardless of causality assessment.

Blood and Hematopoetic: Leukopenia

Cardiovascular: Hypotension and tachycardia

Eye and Ear: Visual disturbances

Gastrointestinal: Dry mouth, nausea, vomiting, and constipation

Nervous System: Hallucinations, CNS depression, CNS stimulation, ataxia, stupor, vertigo, convulsion, and circumoral paresthesia

Psychiatric: Somnolence, confusion, euphoria, depression, dysphoria, depersonalization, anxiety, psychosis, and emotional lability

Miscellaneous and Ill-Defined Conditions: Dizziness, headache, insomnia, abnormal thinking, chest pain, lack of effect, and face edema

SYMPTOMS AND TREATMENT OF OVERDOSE

Signs and Symptoms: Signs and symptoms which might be expected to occur are psychotic episodes including hallucinations, anxiety reactions, respiratory depression and coma (experience with cases of overdosage of more than 10 mg/day has not yet been reported).

Treatment: Overdosage may be considered to have occurred, even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

If psychotic episodes occur, the patient should be managed conservatively, if possible. For moderate psychotic episodes and anxiety reactions, verbal support and comforting may be sufficient. In more severe cases, antipsychotic drugs may be useful; however, the utility of antipsychotic drugs in cannabinoid psychosis has not been systematically evaluated. Support for their use is drawn from limited experience using antipsychotic agents to manage cannabis overdoses. Because of the potential for drug-drug interactions (eg, additive CNS depressant effects due to nabilone and chlorpromazine), such patients should be closely monitored.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

The use of forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or cholestyramine has not been reported. In the presence of normal renal function, most of a dose of nabilone is eliminated through the biliary system.

Treatment for respiratory depression and comatose state consists in symptomatic and supportive therapy. Particular attention should be paid to the occurrence of hypothermia. If the patient becomes hypotensive, consider fluids, inotropes, and/or vasopressors.

DOSAGE AND ADMINISTRATION

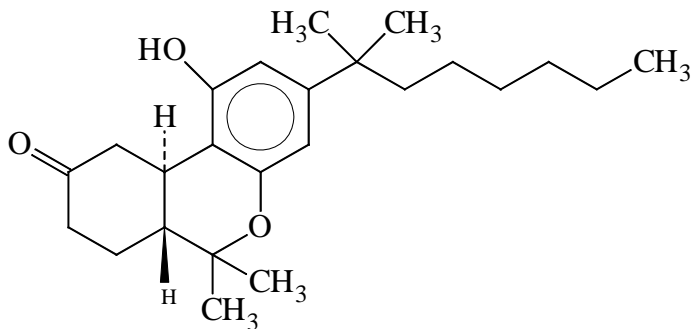
Adults:

The usual dosage of ^NCESAMET[®] (nabilone) is 1 mg or 2 mg twice a day. The first dose should be given the night before initiating administration of chemotherapeutic medication. The second dose is usually administered 1 to 3 hours before chemotherapy. If required, administration of ^NCESAMET[®] can be continued up to 24 hours after the chemotherapeutic agent is given. The maximum recommended daily dose is 6 mg in divided doses.

^NCESAMET[®] is available in 0.25 mg and 0.5 mg strengths for dose adjustment within the therapeutic range. Dose adjustment may be required for the purposes of response and tolerance in individual patients. Overdosage may occur even at prescribed dosages, if disturbing psychiatric symptoms are present. In these cases, the patient should be observed in a quiet environment and supportive measures, including reassurance, should be used. Subsequent doses should be withheld until patients have returned to their baseline mental status; routine dosing may then be resumed if clinically indicated. In such instances, a lower initiating dose is suggested.

^NCESAMET[®] contains nabilone in a capsule dosage form and is intended only for oral administration.

STRUCTURAL FORMULA AND CHEMISTRY



Molecular Formula: C₂₄H₃₆O₃

Molecular Weight: 372

U.S.A.N.: Nabilone

Chemical Name: trans(+)-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one

Description: White crystalline powder

Composition:

Each 1 mg ^NCESAMET[®] capsule contains 1 mg of nabilone, starch, povidone, gelatin, FD&C blue #2 (indigo carmine), red iron oxide, and titanium dioxide.

Each 0.5 mg ^NCESAMET[®] capsule contains: 0.5 mg of nabilone, starch, povidone, gelatin, titanium dioxide, D&C red # 33, D&C yellow # 10, FD&C red # 40.

Each 0.25 mg ^NCESAMET[®] capsule contains: 0.25 mg of nabilone, starch, povidone, gelatin, titanium dioxide, D&C yellow # 10, FD&C blue #1, FD&C red # 40.

Stability and Storage Recommendations:

Store at controlled room temperature at 15-30°C.

AVAILABILITY

^NCESAMET[®] 1 mg capsule: each No. 2 hard gelatin capsule, opaque blue cap and white body, imprinted ICN logo on the cap and 3101 on the body, contains 1 mg of nabilone and are available in bottles of 50 capsules.

^NCESAMET[®] 0.5 mg capsule: each No. 4 hard gelatin capsule, opaque red cap and white body, imprinted ICN logo on the cap and 3102 on the body, contains 0.5 mg of nabilone and are available in bottles of 50 capsules.

^NCESAMET[®] 0.25 mg capsule: each No. 4 hard gelatin capsule, opaque green cap and white body, imprinted ICN logo on the cap and 3103 on the body, contains 0.25 mg of nabilone and are available in bottles of 50 capsules.

^NCESAMET[®] (nabilone) legally is considered to be a narcotic and is subject to the controls which apply to those drugs.

PHARMACOLOGY

Nabilone has neurologic, endocrinologic and cardiovascular activity in animals although these may not be valid predictors of effects in a clinical setting.

Nabilone produces ataxia and hypoactivity; by the oral route, it is twice as active as Δ^9 THC. In rabbits and in rhesus monkeys, doses of 0.064 and 0.01 mg/kg, respectively, caused a modest decrease in blood pressure. Massive doses of 3 mg/kg caused sustained, alternating periods of hypotension and hypertension in rhesus monkeys. Doses of 0.064 mg/kg in dogs caused a modest, delayed increase in blood pressure.

Standard behavioural assays were used to evaluate psychoactive effects. Nabilone slowed muricidal activity in rats, reduced reactivity of septal-lesioned rats, slowed self-stimulation, reduced food consumption and increased reactivity to touch. In most operant conditioning studies nabilone depressed responding.

Nabilone effectively antagonized emetic doses of carmustine and of mechlorethamine in cats. Naloxone antagonized the anti-emetic effect of nabilone in apomorphine or deslanoside-induced emesis in cats.

Nabilone is rapidly absorbed and extensively metabolized in rats, dogs, monkeys and man.

Two major metabolic pathways appear to be involved in the bio-transformation of nabilone. One is the stereo-specific enzymatic reduction of nabilone to two metabolites, the RRS and the SSS carbinols. A second possible metabolic pathway is the direct enzymatic oxidation of the aliphatic side-chain of nabilone, without prior reduction of the 9-keto moiety, to produce hydroxylic and carboxylic analogs.

In the dog, the stereo-specific reduction pathway appears to be the more important, and possibly the only, pathway involved. This probability is supported by the high concentrations of the SSS carbinol metabolite found in dog plasma and brain tissue, as compared to those concentrations found in monkeys.

In the dog, peak plasma concentrations of nabilone and of the SSS metabolite occurred two hours after an oral dose. Carbinol levels were 3 to 4 times greater than those of nabilone, and the combined concentrations accounted for essentially all of the plasma radiocarbon. The concentration of the SSS carbinol in brain tissue was 2 to 4 times greater than that found in plasma. The plasma half-life of nabilone was approximately 2 hours, while that of the radiocarbon and of the metabolite was over 30 hours. Furthermore, after repeated dosing, the SSS carbinol accumulated in brain tissue in the dog, but not in the monkey. It is thought that the presence of these high concentrations of metabolite in plasma and brain over time may have played a role in the toxicity of nabilone observed in the long-term canine study.

In the monkey, the kinetics of nabilone are different from the dog but similar to those in man (see ACTION section). Furthermore, in the monkey and in man, the two metabolic pathways appear to be involved, the more important one also being direct enzymatic oxidation.

Antiemetic Effects of Nabilone in Animals:

The antiemetic activity of nabilone was evaluated in cats against carmustine (BCNU) and mechlorethamine (HN2). Without pretreatment, BCNU at 10 to 20 mg/kg evoked vomiting with an incidence of 50 percent (11 of 22 trials) and an average latency of 145 minutes. In contrast, after pretreatment with nabilone, BCNU failed to cause vomiting in any of 14 trials. HN2 at 5 mg/kg proved to elicit vomiting uniformly and promptly, with an average latency of 15 minutes. In the presence of nabilone, HN2 elicited vomiting in only 2 of 8 trials after the prolonged average latency of 209 minutes.

Nabilone is effective in reducing cis-platinin induced emesis of pigeons. Doses as low as 0.02 mg/kg, I.M., decreased the emetic episodes induced by a dose of 8 mg/kg, I.V., of cis-platinin. Nabilone is approximately 80 to 160 times more potent than prochlorperazine in this test system. Prochlorperazine effectively blocks apomorphine-induced emesis at doses of 0.125, 0.25 and 0.5 mg/kg, I.V. Nabilone, on the other hand, was totally ineffective in blocking apomorphine-induced emesis at doses of 0.008, 0.016 and 0.032 mg/kg, I.V.

HUMAN PHARMACOLOGY

Radiolabeled ¹⁴C-nabilone formulated with PVP was administered orally to two fasted subjects in a 2 mg dose containing 48 μ Ci of radioactivity. The plasma concentration of ¹⁴C-nabilone equivalence reached approximately 10 ng/mL at 1 to 2 hours and then disappeared exponentially with time. After the oral administration of the ¹⁴C-nabilone-PVP formulation, 60 percent of the radioactivity was recovered in feces and 24 percent was recovered in urine for a total recovery of 84 percent.

Intravenous studies were conducted with a solution obtained by dissolving nabilone in ethanol. A 0.5 mg intravenous dose of ¹⁴C-labeled nabilone administered to 5 normal subjects resulted in a mean area under the plasma concentration curve of 90 ng/hr/mL. Approximately 22 percent of

the radioactivity was recovered in urine and approximately 67 percent was recovered in feces. Less than 1 percent was recovered as expired CO₂.

The mean area under the plasma concentration curve after a 2 mg oral dose in two subjects was 345 ng/hr/mL. The percentages of radioactivity excreted in urine and feces after the oral and intravenous administration of nabilone are in good agreement.

This supports the view that most of the oral dose was absorbed. The results further indicate that within the dose range studied, the elimination of the drug was independent of the route of administration and the size of the dose.

¹⁴C-nabilone (0.5 mg, 12 μCi) was administered by the intravenous route to 5 subjects. Plasma concentration of total radioactivity disappeared after dosing in at least a biphasic manner with the initial phase representing uptake and distribution into tissues, while the latter phase presumably represented metabolism and subsequent excretion of the drug.

The alcoholic metabolite forms rapidly and disappears at a slower rate than the parent compound. The mean plasma half life of total radioactivity for the five subjects was 20.6 ± 1.3 hours over a range of 17 to 25 hours.

Chronic oral administration of nabilone 1 mg t.i.d. for 14 days resulted in no significant accumulation of nabilone or carbinol.

TOXICOLOGY

Acute Toxicity:

The oral LD₅₀ of nabilone was >1000 mg/kg in mice, >2000 mg/kg in rats, >1 mg/kg in cats and >5 mg/kg in monkeys. The oral and intravenous LD₅₀ in dogs was higher than 1 mg/kg. Signs

of toxicity included hypoactivity, ataxia and respiratory depression in all species. Dogs given singly intravenous doses of 1 mg/kg promptly became ataxic and lost consciousness for about 48 hours.

Subacute Toxicity:

Rats: Nabilone was administered to rats for 14 consecutive days, at a dose of 0.8 mg/kg, by the intravenous route. Two animals died during the study. Effects seen after dosing included loss of righting reflex, intermittent tonic convulsions, hypnosis, vocalization, Straub tail and hypothermia.

Nabilone was administered in the diet to rats for 92 days, at dosage levels of 6.25, 12.50 and 25.00 mg/kg. Hypothermia was observed in all treated animals during the first 24 hours. During the first week, catatonia and hyperirritability to touch occurred in the high-dose group. Slight to moderate decreases in body weight gains occurred in all treated groups.

Dogs: Intravenous doses of 0.4 mg/kg/day were administered to dogs for 14 days. Effects observed after dosing included hyperirritability to touch, sedation, respiratory depression, fine tremors, ataxia and anorexia. All dogs developed thrombophlebitis at the injection site.

Nabilone also was administered orally for 3 months at dose levels of 0.25, 0.5, and 1.0 mg/kg/day. During the first week, ataxia was seen in the mid and high-dose group and anorexia in the high-dose group.

Chronic Toxicity:

A year-long study in dogs was initiated, but terminated after 7 months due to high mortality. Nabilone was administered orally at dose levels of 0.5, 1.0 and 2.0 mg/kg/day. Eight dogs per dose were treated. Most deaths were preceded by convulsions. No histopathologic lesions were found in the brain or other tissues. The occurrence of convulsions and death in these dogs was believed to be due to the accumulation of a toxic metabolite in the plasma and the brain.

A subacute study in which the toxicity of nabilone was compared to that of SSS carbinol was conducted in dogs. Nabilone and the SSS carbinol were administered daily for five days, intravenously, to 1 male and 1 female per drug, at the dose of 2 mg/kg. One nabilone-treated dog became moribund and was sacrificed on the second day. Anorexia, ataxia, hypoactivity, emesis and shivering were observed in both treated groups. Plasma levels of the SSS carbinol were 27 - 37 times higher than the levels of nabilone. No convulsions occurred. Tissue levels of the SSS carbinol or of nabilone in the brain were not determined.

Doses of 0.0, 0.1, 0.5, and 2.0 mg/kg/day of nabilone were administered by the nasogastric route to Rhesus monkeys for one year. An additional group was given 2.0 mg/kg/day on an intermittent schedule: two-week periods of treatment each followed by an interval of two weeks of treatment. The only changes noted were hypoactivity and sedation which occurred the first two days at the mid- and high-dose levels. Transient periods of anorexia and isolated instances of ataxia and emesis also were noted at the high-dose level.

Teratogenic Studies:

Nabilone was administered orally to pregnant rats on gestation days 6 through 15 at doses of 1, 4 and 12 mg/kg. Hypoactivity and, when handled, hyperirritability and hypertonia were observed during the first three days of treatment. Anorexia and weight loss occurred in all treated groups. Litter size was decreased and resorption incidences increased. The body weights of fetuses from treated animals were slightly reduced.

Nabilone was administered orally to gravid rabbits on gestation days 6 through 18 of 0.7, 1.6 and 3.3 mg/kg. Anorexia and decreased body weight occurred in the mid- and high-dose groups. One rabbit each in the low- and mid-dose groups, and three rabbits in the high-dose, aborted and resorption incidences were increased at the mid- and high-dose levels.

Reproduction Studies:

Nabilone was administered in the diet to rats at dose levels of 1, 4 and 12 mg/kg. Male and female rats were treated, respectively, for 60 and 17 days prior to mating; in females, nabilone

administration continued through mating, gestation and lactation periods. Dose-related decrease in body weight and food consumption occurred in both male and female rats. The mean liveborn litter size in the high-dose group was decreased due to increased number of stillborn.

Perinatal and Postnatal Studies:

Nabilone was administered by gavage to pregnant rats at doses of 1, 4 and 12 mg/kg from gestation day 14 through post-partum day 21. Maternal food intake and body weight gain were decreased in treated dams. Mean litter size and survival values were significantly decreased in the high-dose group: only 4 litters survived through post-partum day 7 and the remainder of the study. Progeny survival in the mid-dose group was slightly decreased. The initial body weights of pups in the mid- and high-dose groups were depressed, and hypothermia was observed in pups from the high-dose group.

Dominant-Lethal Tests in Rats:

Two studies were conducted using the nabilone-PVP co-precipitate, the results were not indicative of a dominant- lethal effect.

Micronucleus Test:

There was no treatment-related effect on the incidence of micronuclei in rat bone marrow polychromatic erythrocytes.

Hypothermia in Rats:

Nabilone produced hypothermia in rats, the response was not significantly altered by differences in the age, sex, or nutritional status of the nabilone-treated rats.

BIBLIOGRAPHY

1. Aapro, M.S., Dupont, D.: Dose-finding study of a new schedule of administration of nabilone (Cesamet), an antiemetic cannabinoid drug. *Cancer Chemother. Pharmacol.*, 1985; 14(Suppl.):S1.
2. Archer, R. A., Blanchard, W.B., Day, William A., Johnson, Douglas W., Lavagnino, E.R., and Ryan, C.W.: Cannabinoids.3.¹ Synthetic Approaches to 9-Ketocannabinoids. Total Synthesis of Nabilone, *J. Org. Chem.*, (June), 1977; 42/13:2277-2284.
3. Borison, H.L., McCarthy, L.E., and London, S.W.: Cannabinoids and emesis, *N. Engl. J. Med.*, 1978; 298/26:1480-1481.
4. Castaner, J., Weetman, D.F.: Nabilone. *Drugs Future (Spain)*, 1978; 3/3:207-210.
5. Craigmill, Arthur L.: Cannabinoids and handling-induced convulsions. *Research Communications in Psychology, Psychiatry and Behaviour*, 1979; 4/1:51-63.
6. Crawford, S.M., Buckman, R.: Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatin: A double blind study. *Med. Oncol. Tumor Pharmacother.*, 1986; 3(1):39-42.
7. Dewey, W.L.: Cannabinoid pharmacology. *Pharmacol. Rev.*, (June), 1986; 38(2):151-178.
8. Dodds, L.: Cancer chemotherapy-induced nausea and vomiting. *Pharm. J.*, (May 10), 1986; 236(6379):588-590.

9. Forest, G.J., Cunningham, D., Hutcheon, A., Moss, R., Young, T. Soukop, M.: Nabilone, prochlorperazine and dexamethasone - Good antiemetic control with few side effects. *Br. J. Cancer*, 1986;54(1):201.
10. Herman, T.S., Jones, S.E., Dean, J., et al.: Nabilone: A potent antiemetic cannabinol with minimal euphoria. *Biomedicine*, 1977; 27:331-334.
11. Herman, T.S., Einhorn, L.H., Jones, S.E., et al.: Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N. Engl. J. Med.*, (June 7), 1979; 300/23:1295-1297.
12. Lemberger, L.: From "grass" roots to clinical utility. *Clin. Pharmacol. Ther.*, (January), 1986; 39(1):1-4.
13. Lemberger, L., and Rowe, H.: Clinical pharmacology of nabilone, a cannabinol derivative. *Clin. Pharmacol. Ther.*, (December), 1975;18/06:720-726.
14. Markham, J.K., Hanasono, G.K., Adams, E.R., and Owen, N.V.: Reproduction studies on nabilone, A synthetic 9-ketocannabinoid. *Toxicol. Appl. Pharmacol.*, 1979; 48/1:A-119.
15. McCarthy, L.E., and Borison, H.L.: Antiemetic activity of nabilone: A cannabinol derivative, reversed by naloxone in awake cats, *Pharmacologist*, 1977; 19/578:230.
16. Nagy, C.M., Furnas, B.E., Einhorn, L.H., and Bond, W.H.: Nabilone (N) antiemetic crossover study in cancer chemotherapy patients. *Proc. Am. Assoc. Cancer Res.*, 1978; 19/118:30.
17. Pomeroy, M., Fennelly, J.J., Towers, M.: Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Cancer Chemother. Pharmacol.*, (July), 1986; 17(3):285-288.

18. Rubin, A., Lemberger, L., Warrick, P., et al.: Physiologic disposition of nabilone, a cannabinol derivative, in man. Clin. Pharmacol. Ther., (July), 1977; 22/1:85-91.
19. Stark, P., and Archer, R.A.: Preclinical pharmacologic profile of a psychoactive cannabinoid. Pharmacologist, 1975; 17:210.
20. Stark, P., and Dews, P.B.: Cannabinoids, I. Behavioural Effects, J. Pharmacol. Exp. Ther., (July), 1980; 214/1:124-130 (July).
21. Stark, P., and Dews, P.B.: Cannabinoids, II. Cardiovascular Effects, J. Pharmacol. Exp. Ther., 1980; 214/1:131-138.
22. Steele, N., Gralla, R.J., Braun, D.W., and Young, C.W.: Double-Blind Comparison of the Antiemetic Effects of Nabilone and Prochlorperazine on Chemotherapy-induced Emesis, Cancer Treat. Rep., 1980; 64/2-3:219-224.
23. Thierman-Duffaud, D.: Antiemetics and anti-neoplastic chemotherapy. (Fr.,Tr.). Sem. Hop. Paris, (May 22), 1986; 62(23):1741-1744.
24. Triozzi, P., Laszlo, J.: Nausea and vomiting. In: Rakel, R.E., Ed., Conns Current Therapy, Philadelphia: Saun 1986. pp.5-9.
25. Ward, A., and Holmes, B.: A preliminary review of its pharmacological properties and therapeutic use. Drugs, 1985, 30(2):127-144.

PART III: CONSUMER INFORMATION**N CESAMET®
nabilone**

This leaflet is part III of a three-part "Product Monograph" published when CESAMET® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CESAMET®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

CESAMET® (nabilone) is indicated for the management of severe nausea and vomiting associated with cancer therapy.

What it does:

CESAMET® decreases nausea (sensation of feeling sick) and vomiting.

When it should not be used:

You should not take CESAMET® if:

- you have known sensitivity to marijuana or other cannabinoid agents
- you have a history of psychotic reactions
- you are under the age of 18 years
- you are breastfeeding
- you are pregnant

What the medicinal ingredient is:

The medicinal ingredient in Cesamet® is nabilone, a synthetic cannabinoid agent.

What the non-medicinal ingredients are:

Cesamet® contains the following non-medicinal ingredients: D&C red #33 (0.5 mg capsule), D&C yellow #10 (0.25 and 0.5 mg capsules), FD&C blue #1 (0.25 mg capsule), FD&C blue #2 (1 mg capsule), FD&D red #40 (0.25 and 0.5 mg capsules), gelatin, iron oxide red (1 mg capsule), povidone, starch, and titanium dioxide.

What dosage forms it comes in:

Cesamet® (nabilone) is formulated into capsules of 0.25 mg, 0.5 mg, or 1 mg strengths for oral administration.

WARNINGS AND PRECAUTIONS **Serious Warnings and Precautions**

- Since CESAMET® will often impair the mental and/or physical abilities required for the performance of potentially hazardous task, you should not drive a car, operate machinery, or perform any activity that requires mental alertness until the effects of CESAMET are no longer present.
- While taking CESAMET®, do not drink alcohol or take other drugs such as sedatives, hypnotics or other substances that can affect the nervous system without consulting with your doctor.
- CESAMET® should be used with extreme caution if you have severe liver dysfunction or a history of non-psychotic emotional disorders.

BEFORE you use CESAMET® talk to your doctor or pharmacist if:

- you are taking any other prescription or non-prescription medicine, or natural/herbal remedies
- you are pregnant or breastfeeding
- you are allergic to nabilone, the main ingredient in CESAMET®, or any other ingredient in CESAMET® (see "What the non-medicinal ingredients are")
- you have hypertension or heart problems

INTERACTIONS WITH THIS MEDICATION

While you are taking CESAMET, do not start any new medicines, including natural or herbal medicines, without speaking to your doctor first. Tell your doctor about all the medicines that you are taking including those that you have bought yourself.

CESAMET can interact with:

- Diazepam
- Sodium secobarbital
- Alcohol
- Codeine
- Any medicine that affects your mental and psychomotor function (e.g., causes hallucinations, weird thoughts, etc).

PROPER USE OF THIS MEDICATION

The label on the container of your medicine should tell you how often to take your medicine and how many doses you should take each time. If not, or if you are not sure, ask your doctor or pharmacist.

Do not take more doses, or take them more often than your doctor prescribes.

Your doctor prescribed CESAMET® for your use only. You should not let anyone else use it.

Usual adult dose:

You will receive CESAMET prior to chemotherapy and, if necessary, after cancer treatment. Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently. Follow the directions provided by your doctor for using this medicine. Your doctor may also have to adjust your dose depending on how you react to CESAMET.

Overdose:

Some of the signs of overdose are psychotic episodes including hallucinations, anxiety reactions, respiratory depression, and coma.

Overdose may even occur at prescribed doses. If psychiatric symptoms (e.g., weird thoughts, hallucinations, etc.) are present, contact poison control centre immediately or go to the nearest emergency room.

Missed Dose:

If you forget a dose of CESAMET[®], you should take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. **Do not** double your dose.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Uncommon	Confusion			✓
	Depression		✓	
	Dissociation			✓
	Headache	✓		
	Orthostatic hypotension		✓	
	Nightmares		✓	
	Seizure			✓
	Tachycardia		✓	
	Tremors		✓	

This is not a complete list of side effects. For any unexpected effects while taking CESAMET[®], contact your doctor or pharmacist immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some patients may experience drowsiness, psychological high, vertigo, dry mouth, depression, ataxia, asthenia, blurred vision, sensation disturbance, anorexia, headache, orthostatic hypotension, euphoria, and hallucinations. You should tell your doctor or pharmacist about these symptoms.

If your nausea (feeling of sickness) or vomiting do not improve while taking CESAMET, consult your doctor for further advice.

If you feel unwell or have any symptoms that you do not understand, you should contact your doctor immediately.

HOW TO STORE IT

Keep CESAMET[®] out of reach of children. Store it at room temperature (15 to 30°C) in the package it came in.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Common	Drowsiness		✓	
	Dry mouth	✓		
	Euphoria		✓	
	Hallucinations			✓
	Somnolence		✓	
	Vertigo		✓	

REPORTING SUSPECTED SIDE EFFECTS

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

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

Online: www.healthcanada.gc.ca/medeffect

By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:

Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada, at:
1-800-361-4261

This leaflet was prepared by Valeant Canada limitée/Limited
Montreal (Quebec) H4R 2P9

Last revised: March 17, 2009