DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

APR 25 1986

Mr. John Lawn
Administrator
Drug Enforcement Administration
1405 I Street, N.W.
Washington, D.C. 20537

Dear Mr. Lawn:

Pursuant to the requirements of the Controlled Substances Act, 21 U.S.C. § 801 et seq., the Food and Drug Administration (FDA) has conducted a scientific and medical evaluation of the drug nabilone. FDA has performed the eight factor evaluation required by 21 U.S.C. § 811 and recommends that nabilone be placed in Schedule II of the Controlled Substances Act. I concur with FDA's recommendation to place nabilone in Schedule II. You will find enclosed a document that supports this recommendation and provides the required eight factor evaluation. Therefore, the Drug Enforcement Administration may now initiate proceedings to control nabilone under the Controlled Substances Act.

Should you have any questions regarding this recommendation, please contact James C. Shehan of FDA's Office of Health Affairs at (301) 443-1382.

Sincerely yours,

Donald Ian Macdonald, M.D.
Acting Assistant Secretary for Health

Enclosure

Basis for Recommendation to Control Nabilone
into Schedule II of the
Controlled Substances Act

Nabilone is a synthetic benzopyran molecule which is pharmacologically related to delta-9-THC. Chemically nabilone is (+)-trans-3(1,1-dimethylheptyl(-6,6a, 7,8,10,10a-hexahydro-1-hydroxy-6-6-dimethyl-9H-dibenzo(b,d)pyran-9-one. Nabilone has been in clinical trials since 1974. A New Drug Application for the indication of alleviation of nausea and vomiting associated with cancer chemotherapy was filed on February 16, 1982. The Food and Drug Administration has concluded that nabilone is a safe and effective drug under the provisions of the Federal Food, Drug and Cosmetic Act.

The abuse potential of nabilone and the need for scheduling nabilone was discussed by FDA's Drug Abuse Advisory Committee on April 28, 1983. Presentations for the Eli Lilly Co. on the abuse potential of nabilone were made by Dr. Lou Lemberger and Dr. Jack Mendelson. Additionally, Dr. Dorothy Dobbs spoke on the central nervous system side effects observed in the clinical trials. The data which these speakers discussed may be found in Factor I of this document. Dr. Donald Jasinski of the Addiction Research Center also presented the results of unpublished studies comparing nabilone to delta-9-tetrahydrocannabinol (delta-9-THC). Dr. Jasinski's data and conclusions can also be found in the body of the document under Factor No. 1.

Dr. Frank Vocci of the FDA summarized the animal pharmacology and clinical studies with respect to the abuse potential of nabilone. He concluded that nabilone has a potential for abuse similar to delta-9-THC. He further concluded that the subjective central nervous system effects of nabilone overlap the recommended therapeutic dosage range. He recommended that nabilone be scheduled and that its schedule be linked to the previous delta-9-THC recommendation. That is, that nabilone should be placed in Schedule II of the Controlled Substances Act similar to the recommendation for delta-9-THC. However, Dr. Vocci said that if the committee found that delta-9-THC should be rescheduled to Schedule III, nabilone could also be placed in Schedule III.

There was an extended discussion of the pharmacology and abuse potential of nabilone vis a vis the previous recommendation of the Drug Abuse Advisory Committee to reschedule delta-9-THC to Schedule II at the time of marketing. One argument made was that the abuse potential of the cannabinoids was in the range of alcohol and the opiates. This was based on clinical observations of individuals who requested treatment for addiction to cannabis at various drug treatment centers around the country. It was argued that nabilone may produce a psychological dependence similar to that observed with cannabis and, therefore, nabilone should be a Schedule II drug. Another argument followed that the abuse potential of marijuana was such that one person in ten developed health problems and life problems from the chronic use of marijuana. These data were obtained from a 10-year follow-up study of marijuana smokers in St. Louis and reported to the committee by Dr. Donald Goodwin. He reasoned that approximately one person in ten would develop a

dependence to marijuana and that substances similar in abuse potential to marijuana would have a high potential for abuse.

Dr. Robert Balster presented an argument which compared the pharmacology of nabilone and delta-9-THC to the opiates, cocaine and the barbiturates. He reasoned that the decision to schedule nabilone should be based upon the scheduling criteria as set forth in the Controlled Substances Act. Dr. Balster concluded that a physical dependence has not been demonstrated with nabilone or delta-9-THC. Therefore, it would be inappropriate to attempt to schedule the drug on its physical dependence characteristics, since they are non-existent. Dr. Balster then reasoned that the psychological dependence capacity would be the basis for a scheduling decision. Dr. Balster reasoned that the psychological dependence capacity of delta-9-THC and nabilone was less than that observed with the opiates, the short-acting barbiturates and cocaine. He believed that nabilone has a psychological dependence capacity of a low-to-moderate intensity as opposed to a severe intensity observed with the barbiturates, cocaine and opiates. He agreed that nabilone has abuse potential but felt that nabilone could appropriately be scheduled into Schedule III or IV. He further stated that he believed the original recommendation to place THC in Schedule II was an incorrect recommendation if one strictly applies the scheduling criteria.

A motion was made to schedule nabilone into Schedule III of the Controlled Substances Act. The motion carried by an 11-2 vote. The committee voted on a second motion, that is, a conclusion that delta-9-THC and nabilone are pharmacologically similar. The motion carried with 12 affirmative votes and one abstention.

The Food and Drug Administration has taken into consideration the counsel of its Drug Abuse Advisory Committee (DAAC) and recommends that nabilone be scheduled into Schedule II of the Controlled Substances Act. The DAAC recommendation is ambiguous insofar as a conclusion that nabilone and delta-9-THC are pharmacologically similar is inconsistent with recommending a Schedule III placement. This is based on the fact that a previous DAAC recommendation (June, 1981) not overturned or reconsidered at the April 28, 1983 meeting, advised the agency to recommend Schedule II placement for delta-9-THC at the time of marketing approval. The basis for the recommendation of nabilone into Schedule II is given in this document (vide infra).

Pursuant to Section 201, subsection b of the Controlled Substances Act, the eight factors are addressed as follows:

1. Its actual or relative potential for abuse.

Nabilone was evaluated for morphine-like activity in the non-dependent and morphine-dependent chronic spinal dog. Delta-9-THC, nabilone, and nantradol had antinociceptive activity in the flexor and skin twitch tests. Also noted for all three drugs was hypothermia, mydriasis and behavioral calming. These effects were not antagonized by naltrexone. Delta-9-THC, nabilone, and

nantradol suppressed withdrawal signs in morphine-dependent dogs undergoing withdrawal. The results suggest some common actions between morphine and cannabinoids although there is no evidence that the cannabinoids interact with an opioid receptor mechanism.

The ability of nabilone to suppress morphine withdrawal in morphine-dependent monkeys was tested in the Committee on Problems of Drug Dependence (CPDD) program. Nabilone partially suppressed the signs of retching and vomiting in the single dose substitution test in morphine-abstinent monkeys. The signs of ptosis, pupillary dilatation, ataxia and decreased responsiveness to stimulation by observers were also reported. Nabilone is not a morphine-like agonist in the morphine-dependent monkey.

Acute administration of nabilone in non-dependent monkeys resulted in ptosis, dozing, mydriasis, ataxia and a reduced responsivity to stimulation from observers and cagemates. The constellation of drug-induced signs was scored and a dose-effect curve was determined. Nabilone was approximately 1/2 as potent as levonantradol and 5 times as potent as delta-9-THC in producing acute effects.

A chronic (30-day) administration study in monkeys utilized an escalating dose regimen, starting at 0.3 mg/kg every 12 hours and finishing at a dose of 30 mg/kg every 6 hours. Tolerance developed to the acute effects. Initially, some effects could be restored by 1/4 log dose escalations; however, beyond a dose of 1.7 mg/kg (day 13), further dose increments had no effects on scored signs. Although the signs were absent, animals did not appear normal as they were often found lying prostrate on the cage floor. Doses as high as 170 mg/kg of nabilone had no effect on animals receiving 30 mg/kg/6 hrs. These monkeys also demonstrated cross-tolerance to delta-9-THC or levonantradol. There was minimal, if any, cross-tolerance to morphine.

Naloxone challenge failed to precipitate withdrawal signs. Abrupt discontinuation of nabilone also failed to elicit signs of an abstinence syndrome.

In separate studies, codeine-lever trained rhesus monkeys failed to self-administer nabilone ($3.2 \times 10^{-4}$ to $3.2 \times 10^{-2}$ mol/kg/injection, delta-9-THC ($10^{-3}$ to $10^{-1}$ mol/kg/injection), or levonantradol (doses not legible from figure).

Clinical studies

The abuse potential of nabilone in human psychopharmacology trials was studied by three separate investigators: Lemberger et al, Mendelson, and Jasinski. In the study by Lemberger, Pence and Forney, 6 healthy male volunteers who were experienced marijuana smokers were assigned 1 of 5 treatments in a 5-way crossover design. The treatments compared oral and i.v. nabilone, oral and i.v. delta-9-THC and placebo.

The study was conducted in a double-blind manner with a repeated measures design blocking over subjects. Treatment orders were randomly assigned to eliminate any order effect. The treatments were administered over a 3-week period with treatments separated by at least 3 days. Each subject received: (1) placebo orally and i.v., (2) nabilone (2 mg, p.o.) and placebo i.v.; (3) THC orally at a dose of 17.5 mg and placebo i.v., (4) placebo orally and nabilone (0.25 mg, i.v.); and (5) placebo orally and THC (2.2 mg, i.v.).

Dosages were selected for oral administration to be those commonly employed for antiemetic dosing. Intravenous doses were selected on the basis of prior information available to the sponsor (Lilly), and interest in maintaining an oral/parenteral ratio of 9/1.

Subjects were monitored every 30 minutes for changes in supine and standing blood pressure for eight hours following drug administration. Pulse rate was monitored at 15-minute intervals for 4 hours and at 30-minute intervals for the remaining four hours of the test session. Subjective effects of the treatments were assessed by subjects completing a modified Cornell Medical Index (CMI) questionnaire and an Addiction Research Center Inventory (ARCI) scale every 15 minutes for the first 4 hours and every 30 minutes for the remaining 4 hours of the test session. Subjects were also observed for objective signs, and a tape recording of discussions with the subjects regarding their experience during each experimental session was made. Subjects were also asked to write a description of the effects of each experimental session. At the end of the five sessions each subject was asked to relate which treatment he preferred.

As expected, active treatments elevated standing and supine heart rates. The effects were statistically significant ($p < 0.001$) when the standing and supine heart rate means were compared using Duncan's new multiple range test. Delta-9-THC (i.v.) produced the greatest increase and was significantly different from all other treatments. Nabilone (i.v.) produced the next largest increase and was significantly different from the three remaining treatments.

Subjective assessments using the ARCI questionnaire failed to demonstrate differences in most instances. However, the Cornell Medical Index (CMI) was more sensitive to differences in drug effects with respect to both "total" score and a "high" subset. Differences in time-action curves and time to maximal response were also observed. Intravenous administration of delta-9-THC and nabilone achieved the highest mean responses. These effects occurred early in the study (1-2 hours) whereas the oral formulations achieved their peak effects at 2-3 hours. A greater CMI "high" score was achieved by i.v. delta-9-THC compared to i.v. nabilone at one hour. Additionally, these two treatments differed significantly from the oral preparations and placebo.

The subjective effects of nabilone did not equal or surpass those elicited by delta-9-THC within routes of administration. However, except for the one-hour i.v. time points, these differences did not achieve statistical significance .

In terms of subject preference, the treatments were ranked THC (i.v.) nabilone (i.v.) nabilone oral THC oral placebo. All active treatments were significantly different from placebo (p 0.05) but there were no statistically significant differences among the active treatments.

The sponsor concluded that nabilone does not appear to produce an equal degree of euphoria as delta-9-THC when compared by a similar route of administration. This conclusion is based on a single dose comparison; thus, euphorigenic potential at equipotent doses was not necessarily assessed. The agency believes it is equally plausible that differences in euphoria within routes of administration may reflect potency differences rather than differences in intrinsic activity.

The second study, conducted by Dr. Mendelson, utilized 3 groups of marijuana smokers (occasional, intermittent, or regular) to discriminate possible differences between nabilone, delta-9-THC, and marijuana in the production of subjective effects. Subjects were also offered an operant paradigm in which to work for preferred drug or money.

The study group was comprised of 24 healthy adult male marijuana smokers between the ages of 21 and 30 years-old. Each subject served as his own control in a consecutive 5-day study in which the following treatments were administered: nabilone (2 mg), nabilone placebo, a standardized marijuana cigarette (1 gm containing 2% delta-9-THC), a standardized marijuana placebo cigarette, delta-9-THC capsules (17.5 mg) and delta-9-THC placebo capsules. Each subject received one active drug and two placebos on each drug day. Treatments were counterbalanced so as to control for order effects. Additionally, treatment days were color coded so that subjects could choose their preferred treatment for the operant paradigms.

Subjects successfully discriminated active treatments from placebos. Regular users of marijuana ranked "highs" as follows: marijuana cigarette oral THC oral nabilone. Intermittent marijuana smokers expressed the same ranking order whereas occasional users reported equivalent degrees of intoxication following marijuana, THC and nabilone administration.

All regular users preferred marijuana cigarettes. All intermittent users prefered marijuana except one who preferred delta-9-THC. Five of the occasional users selected marijuana and the other three did not work for any drug.

Dr. Mendelson concluded that nabilone was considerably less reinforcing than marijuana or delta-9-THC.

This study is flawed in a manner analogous to the Lemberger study. In order to make conclusions about differences in intrinsic activity, equipotent dosages should be used. As single doses of delta-9-THC, nabilone and marijuana were used, potency differences may account for differences seen among drug "high" values.

Jasinski of the NIDA Addiction Research Center recently completed studies assessing the abuse potential of nabilone relative to delta-9-THC and morphine (unpublished data). Findings of this research study were presented at the April 28, 1983 meeting of the DAAC. Initially, delta-9-THC capsules (20 mg) were compared to marijuana cigarettes. Subjects reported that this dose of delta-9-THC was equivalent to 1-1/2 marijuana cigarettes. However, delta-9-THC had a slower onset than the cigarette. Both delta-9-THC capsules and the marijuana cigarettes, but not placebo, produced "euphoria" scores equivalent to 15 mg of morphine as measured on the MBG (Morphine Benzedrine Group) scale. However, subjects were able to discriminate delta-9-THC from morphine. It should be noted that diazepam and dextropropoxyphene are also capable of generating MBG scores equivalent to 15 mg of morphine.

In a second experiment, subjects were administered morphine (30 mg, s.c.), delta-9-THC (20 mg, p.o.), nabilone (8 mg p.o.) or placebo. Delta-9-THC and nabilone had similar onsets, but the duration of action of nabilone was longer. Nabilone and delta-9-THC were identified by subjects as "pot".

The highest dose of nabilone (8 mg) produced dysphoric feelings as measured on the psychopharmacologic rating scales known as the LSD and PCAG subscales. This suggests that there is a dose or dose-range that might limit acute nabilone intake.

Valid potency estimates of delta-9-THC and nabilone were constructed for the self-reported items of "feel the drug", "number of joints equivalent", "subjects liking" and MBG subscale. The geometric mean of the potency ratio of these scales was about 7; i.e., nabilone was about 7 times as potent a euphoriant as delta-9-THC. (It should be noted that the comparisons of nabilone and delta-9-THC in the Lemberger et al and Mendelson studies used delta-9-THC doses which were 8.5 times the nabilone dose. This strengthens the argument that the slight differences observed in subjective effects may be accounted for by a more than equipotent dose of delta-9-THC).

Jasinski concluded that nabilone and delta-9-THC are very similar in producing subjective effects. Nabilone had a similar onset but a longer duration than delta-9-THC. Nabilone was about seven times as potent as delta-9-THC in producing subjective effects.

The Eli Lilly Company also submitted results of clinical pharmacology studies with respect to the abuse potential of nabilone. A 5 mg dose was more reliably euphorigenic than 2.5 mg in "IND protocol #1." However, the small number of subjects (n = 3) precluded a firm conclusion. Further studies (IND protocol #2) noted a rapid development of tolerance when nabilone (2 mg, b.i.d.) was administered for seven days.

Some euphoria breakthrough was noted with a dose of 5 mg. Partial loss of tolerance occurred within one week; the 5 mg dose approximately doubled the CMI score of the previous 5 mg dose. Abrupt discontinuation of a one-week regimen of 2 mg of nabilone, b.i.d., did not result in a withdrawal syndrome.

In a second study where nabilone (1 mg, b.i.d.) was administered for two weeks, 2/6 subjects initially experienced euphoria for the first days; thereafter, tolerance developed to the effect. The magnitude of tolerance development was not quantified.

An intravenous study (IND protocol #3) was conducted in eight subjects. Of five subjects who received 0.5 mg of nabilone, three of these subjects experienced euphoria, dizziness and dry mouth.

The frequency of CNS effects of nabilone occurring in the recommended therapeutic range in a patient population can be inferred from clinical trials data. The protocol numbers referred below are those found in the New Drug Application for nabilone.

Protocol #20.

This multicenter protocol assessed nabilone (2 mg, every 12 hours) given for a 1 to 5 day chemotherapy cycle compared to 10 mg of prochlorperazine administered every 12 hours.

a. Dr. Young treated 58 patients with nabilone and 53 patients with prochlorperazine. The nabilone group experienced the following incidence rates of adverse reactions: drowsiness (39.7%), vertigo (39.7%), dry mouth (27.4%) and a high feeling (19%). Other nabilone effects included asthenia, decrease in concentration, excessive appetite, sleep disturbance, headache and hypotension (3/58 patients). The prochlorperazine group reported a 50% side effect incidence with drowsiness (26.4%), vertigo (13.2%) and dry mouth (3.8%) occurring with the highest rates.

b. Dr. Einhorn's study involved 43 patients on nabilone and 42 on prochlorperazine. Side effects observed in the nabilone group were drowsiness in 18 patients (41.9%), a high feeling in 17 (39.5%), and vertigo in 15 (34.9%). Similar reactions in the prochlorperazine group included 3 (7.1%) with drowsiness, a "high" feeling in 1 patient and vertigo in 1 (2.4%) patient.

c. The third part of the multicenter study was conducted by Dr. Bressler. Only 10 patients were enrolled. One patient discontinued treatment because of severe hallucinations.

Side effect results were tabulated across the three studies; the incidence of the most common adverse reactions is reproduced below:

| Adverse Reaction | Nabilone (111) | Prochlorperazine (103) |
|---|---|---|
| Drowsiness | 43 (38.7%) | 18 (17.5%) |
| Vertigo | 41 (36.9%) | 8 ( 7.8%) |
| "High" Feeling | 29 (26.1%) | 4 ( 3.9%) |
| Dry Mouth | 18 (16.3%) | 2 ( 1.9%) |
| Asthenia | 10 ( 9.0%) | 4 ( 3.9%) |
| Hallucinations | 4 ( 3.6%) | 0 ( 0.0%) |

Protocol 28

This multicenter (6) study compared the antiemetic effects of a fixed dose of nabilone (2 mg) administered every 12 hours to placebo. Of the 199 patients entered into the study, 183 patients received at least one dose of nabilone. The FDA tabulated the following side effect incidence for the nabilone-treated group:

| Side Effect | No. of patients | % |
|---|---|---|
| Vertigo | 102 | 55.7 |
| Drowsiness | 96 | 52.5 |
| Dry Mouth | 57 | 31.1 |
| Ataxia | 20 | 10.9 |
| Depersonalization syndrome | 18 | 9.8 |
| Euphoria | 17 | 9.8 |
| Sleep Disturbance | 16 | 8.7 |
| Dysphoria | 14 | 7.7 |

The psychiatric effects (depersonalization syndrome, euphoria, dysphoria) were described by the study oncologist and a psychiatric consultation was not made. It was noted that patients recovered after stopping nabilone therapy.

Summary:

Nabilone is both chemically and pharmacologically similar to delta-9-THC. As with delta-9-THC, tolerance development is rapid and of a large magnitude. In the dog, typical descriptions of delta-9-THC-like static ataxia are reported for nabilone. These effects fade rapidly during chronic dosing, indicating rapid tolerance development. In the monkey, nabilone produced signs of ptosis, dozing, mydriasis, ataxia and reduced responsivity to stimulation. These signs were reproduced by administration of delta-9-THC or levonantradol, the only differences being in drug potency. A 3-log shift to the right occurred with chronic nabilone (3 weeks) dosing, indicating a high magnitude of tolerance. Cross-tolerance to delta-9-THC and levonantradol but not morphine was demonstrated.

In separate experiments, nabilone was administered to morphine-dependent monkeys undergoing withdrawal in the single dose substitution test. Partial alleviation of signs was observed. However, this cannot be interpreted to infer that nabilone has morphine-like agonist properties. Other evidence that nabilone is lacking in morphine-like properties includes lack of precipitation of withdrawal by naloxone in nabilone-treated monkeys and lack of cross tolerance to morphine.

Three human psychopharmacology studies conducted by Lemberger et al, Mendelson, and Jasinski were reviewed. Although nabilone was found to produce less subjective effects than delta-9-THC in the Lemberger and Mendelson studies, these conclusions were based on single dose comparisons. Thus, there is a common flaw in both studies in that a potency ratio was not established.

Euphorigenic potential differences should be assessed at equipotent doses. Although the doses used may be approximately equipotent, the differences seen may reflect differences in potency rather than differences in intrinsic activity.

Mendelson's finding that marijuana was the preferred drug among subjects in his study points out that nabilone would probably be a secondary choice as a drug of abuse. However, preference between equipotent doses of delta-9-THC and nabilone may not exist.

Jasinski compared nabilone with delta-9-THC. Subjects could not discriminate nabilone from delta-9-THC. Nabilone was seven times as potent as delta-9-THC in producing subjective "euphoria"-like responses.

Other human studies evaluated by the sponsor suggest that supratherapeutic doses (5 mg) are more reliably euphorigenic than the proposed clinical dose of 2 mg. Tolerance developed to the CNS subjective effects within 7 days of daily intake. An assessment of both placebo-controlled and prochlorperazine controlled studies in patients receiving nabilone as an adjunct to cancer chemotherapy leads to the conclusion that subjective CNS effects occur at clinical doses (2 mg, b.i.d.).

2. Scientific evidence of its pharmacologic effect, if known.

The effect of nabilone on spontaneous and schedule-controlled behavior was studied in mice, rats, cats, dogs and monkeys and rats, pigeons, monkeys, respectively. The general effect on spontaneous motor activity and the normal behavioral repertoire of the animals was CNS depression. The effects of nabilone on schedule-controlled behavior were complex, variable at times, and probably both species and paradigm-specific.

Nabilone was active in two analgesic screens, the acetic-acid writhing model in mice and the tail-jerk test in rats. The effects of nabilone were not antagonized by naloxone. Additionally, the effects of morphine were not antagonized by nabilone. From these data it appears that nabilone does not produce antinociception through a direct opiate receptor mediated mechanism nor is it an opiate antagonist.

Nabilone and delta-9-THC were compared for inhibitory effects on prolactin release in rats pretreated with 5-HTP and fluoxetine. Both nabilone and delta-9-THC decreased prolactin release in 5-HTP treated rats.

The acute toxicity of nabilone was investigated in five species. Signs of toxicity in mice and rats were hypoactivity, limb weakness, slow respiration, hyperirritability when handled, catalepsy, hypothermia and diuresis. Mice had, in addition, straub tail and signs of ptosis. The oral $LD_{50}$ in mice was estimated to be between 1000 and 2000 mg/kg; the $LD_{50}$ in rats was greater than 2000 mg/kg.

Cats administered 1 mg/kg doses of nabilone, p.o., had mild ataxia and slight mydriasis which began 1 hr after dosing and persisted for 3 to 4 hours.

Dogs were administered nabilone, 1 mg/kg, p.o. in three dosage forms: (1) as a suspension in aqueous 1% tween 80 vehicle; (2) as a polyvinylpyrrolidone (PVP) co-precipitate; or (3) as a formulation of nabilone/lactose (or starch) in a 1:9 ratio. The first two formulations produced ataxic effects at two hours whereas the third formulation was without effect. Dogs given nabilone-PVP at a dose of 5 mg/kg developed mydriasis, slow pupillary responses to light, ataxia and sedation within one to three hours of dosing. Other early effects seen infrequently were myoclonus, retching, emesis, salivation, dry mouth, hyperirritability to sound, and one tonic seizure (one dog). All animals survived and presented with signs of ataxia, lethargy and slow pupillary responses to light at 25 hours. Toxic signs resolved gradually on the second through fourth days. Dogs given single i.v. doses of nabilone (in an ethanol vehicle), 1 mg/kg, became ataxic within 10 minutes and lost consciousness for 48 hours. Upon regaining consciousness, animals were anorectic for an additional 48 hours but were normal in appearance by the fifth day of dosing.

Two rhesus monkeys (one male, one female) were administered 5 mg/kg nabilone (in a 1% tween 80 vehicle) by nasogastric intubation. The female was slightly ataxic 1-1/2 hours after dosing but was normal by 3 hours. The male was unaffected. Rhesus monkeys tolerated single 10 mg/kg doses of nabilone when given as the PVP co-dispersion. Animals became hypoactive and sedated within 15 to 30 minutes and remained in this condition during the first day. By day 2, the animals appeared normal.

Subchronic toxicity studies of nabilone by the intravenous and oral routes were conducted in the rat. In the 14-day i.v. study (R-374) toxic signs diminished by the fourth day, suggesting tolerance development. In the 92-day feeding study (R-1003) nabilone was administered at doses of 6.25, 12.5 or 25 mg/kg. The high dose group was hyperirritable to touch and catatonic during the first week of the study. These signs rapidly resolved, again suggesting tolerance development to nabilone. A second feeding study in Fisher 344 rats (R-418) utilized dietary concentrations of 0.00156, 0.00625, 0.0250 or 0.1 percent nabilone which provided average daily doses of 1, 5, 19, and 93 mg/kg. Animals in the three upper dose groups exhibited hyperactivity during the first three weeks. In the 5 mg/kg group, rats remained hyperactive throughout the study whereas the upper two dose groups exhibited hypoactivity throughout the rest of the dosing period.

In the dog, the subchronic toxicity of nabilone was evaluated by oral and i.v. routes of administration. A 92-day study of oral nabilone (at 0.25, 0.5, and 1.0 mg/kg/day) in beagle dogs observed that ataxia was produced during the first week (D-4013). This effect was not noted after the second week, indicating rapid development of tolerance. A higher dose range (0.5, 1.0 and 2.0 mg/kg) was used in the second oral nabilone study (D-3558). Several effects were observed during the first three weeks of the study to which tolerance developed: hypoactivity, ataxia, anorexia, hypothermia, moderate-to-severe tear flow reduction, and conjunctival hyperemia. Mydriasis was a persistent effect during the first four months. At 7 months, cumulative toxicity caused termination of the study. Two, 6, and 7 dogs, in the low,

medium and high-dose groups (n = 8 dogs/group), respectively, had died or were sacrificed in a moribund condition. Convulsions often preceded death. Of note, gradual deterioration of the animals' conditions was not observed.

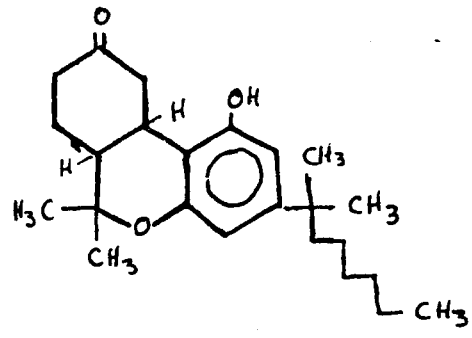
An intravenous toxicity study of nabilone in dogs utilized a fixed dose of 0.4 mg/kg (D-3374). Signs of drug effect included anorexia, hyperirritability to touch, decreased respiration, sedation, fine tremors and ataxia. All signs, except anorexia, diminished between the third and fifth day of dosing. Animals were tolerant for the remainder of the study except for a transient mild ataxia occurring immediately after dosing. A five-day i.v. toxicity comparison of nabilone and its SSS-carbinol metabolite was performed in beagle dogs (2 mg/kg, both drugs). Signs of CNS depression were noted with either drug. Plasma samples taken from dogs in both groups revealed that SSS-carbinol to nabilone ratios were 22 to 37, indicating that the SSS-carbinol-treated group had blood levels of drug about twice those found in nabilone treated dogs.

A one-year study of the toxicity of nabilone by the nasogastric route of administration was performed in rhesus monkeys (M-6080). Three males and three females per group received either 0, 0.1, 0.5 or 2.0 mg/kg of nabilone/day; a fifth group was given 2.0 mg/kg/day on an intermittent basis. Sedation and hypoactivity were observed in groups dosed above 0.1 mg/kg. Single episodes of emesis and ataxia were observed in the high-dose group. Tolerance developed rapidly to the CNS effects.

Summary: The most consistent effect of nabilone observed across species is mild CNS depression, manifested by hypoactivity and ataxia. Tolerance usually develops rapidly to the CNS depressant effects of nabilone.

3. The state of current scientific knowledge regarding the drug or other substance

Nabilone is a hexahydrodibenzopyranone related to delta-9-THC. The structural formula is:




Nabilone differs from delta-9-THC by the 9-keto function and the dimethylheptyl side chain. The New Drug Application for nabilone is for the indication of alleviation of nausea and vomiting caused by chemotherapeutic agents used in the treatment of cancer.

4. Its history and current pattern of abuse

As nabilone is not marketed in this country, no data are available regarding abuse patterns.

5. The scope, duration and significance of abuse

As nabilone is not marketed in this country, no data are available regarding abuse patterns.

6. What, if any, risk there is to the public health.

Nabilone presents a moderate-to-severe risk to the public health. There is a risk to the individual with respect to psychological dependence. However, it is doubtful that nabilone would successfully compete with, or replace, smoking marijuana as the preferred means of obtaining a cannabinoid-like "high". This is because of 1) the contrast of the rapid onset of pharmacologic effects with marijuana as opposed to nabilone ingestion with delayed onset; 2) the longer duration of nabilone's pharmacologic effects; and 3) the inability to titrate the subjective effects following nabilone ingestion.

Nabilone also presents a risk to individuals who would operate heavy machinery or drive a car while on nabilone therapy. It is a safe assumption that individuals abusing the drug at higher doses would have greater impairment and, therefore, present a greater risk to themselves and others while operating machinery or driving a car. It is not yet known whether it is possible to "spike" cigarettes with nabilone and obtain a more rapid onset of effects. If this were the case, nabilone could be similar in abuse potential to marijuana.

7. Its psychic or physical dependence liability

Nabilone has not demonstrated any physiologic dependence in animal tests or the limited human experience to date.

The psychopharmacologic effects of nabilone indicate that it may produce severe psychological dependence. The level of dependence may be equal to that observed with delta-9-THC, which is considered capable of producing severe psychological dependence.

8. Whether the substance is an immediate precursor of a substance already controlled under this title

Nabilone is not an immediate precursor of a substance already controlled under this title.

Recommendations:

1. The Food and Drug Administration concludes that the abuse potential and psychological dependence capacity of nabilone are consistent with a placement into the Controlled Substances Act. The issue of the appropriate schedule for

nabilone has been discussed in an open public advisory session (DAAC meeting, April 18, 1983) and the agency was advised to recommend a Schedule III placement. Further, the DAAC concluded that nabilone and delta-9-THC are pharmacologically similar. However, the DAAC was disinclined to reverse a previous recommendation that delta-9-THC be controlled as a Schedule II drug upon marketing. Thus, the agency was left with a less than clear opinion from the DAAC. Nabilone is being recommended for Schedule II status as the agency conclusion, and also that of the DAAC, is that nabilone and delta-9-THC are very similar psychoactive substances. The agency further concludes there are no meaningful differences in abuse potential between nabilone and delta-9-THC. Accordingly, the individual criteria are addressed below:

A. The drug or other substance has a high potential for abuse.

Nabilone has a potential for abuse that is essentially indistinguishable from that of delta-9-THC. Nabilone differs from delta-9-THC in that it is more potent and longer lasting. However, in terms of production of psychic effects, nabilone and delta-9-THC are equivalent.

B. The drug or other substance has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.

The marketing approval of nabilone under the Federal Food, Drug, and Cosmetic Act is consistent with a currently accepted medical use in treatment in the United States.

C. Abuse of the drug or other substance may lead to severe psychological or physical dependence.

The psychological dependence capacity of nabilone is not known with absolute certainty but can be inferred from the pharmacological equivalence to delta-9-THC. As delta-9-THC is considered to be the major psychoactive principle in marijuana, and marijuana is capable of producing severe psychological dependence, then delta-9-THC must also be capable of producing severe psychological dependence. Similarly, nabilone would be inferred as being capable of producing severe psychological dependence due to its pharmacological equivalence to delta-9-THC.

Nabilone is currently believed to lack physical dependence capacity.

Nabilone should be classified as an hallucinogenic drug.

The agency has concluded that nabilone and delta-9-THC are pharmacologically equivalent. Currently, delta-9-THC is classed as a Schedule I hallucinogen in Section 202(c) of the CSA. Nabilone possesses all the psychoactive effects of delta-9-THC. Indeed, 16 of the 531 patients in the nabilone clinical trials experienced hallucinations. Thus, based on pharmacological equivalence and legal classification, nabilone should be classified as an hallucinogenic drug.