U.S. Department of Justice

Drug Enforcement Administration

Schedules of Controlled Substances: Placement of Amineptine into Schedule I

Background, Data, and Analysis:

Eight Factors Determinative of Control

and Findings Pursuant to 21 U.S.C. 812(b)

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INTRODUCTION

Amineptine is a synthetic antidepressant with central nervous system stimulant effects and has no approved medical use and no known therapeutic application in the United States. There are numerous reports of clinical cases of amineptine abuse and dependence in countries where amineptine has been prescribed for medical use. Pursuant to its obligations under the Controlled Substances Act (CSA), the Department of Human Health Service (HHS) published two Notices in the Federal Register. The first Notice requested public information to be considered by the World Health Organization (WHO) in preparing its scientific and medical evaluation for amineptine, and the second Notice solicited public comment regarding a recommendation by WHO to impose international controls on amineptine[1]. In 2003, the United Nations Commission on Narcotic Drugs (UN/CND), at the advice of the Director-General of the WHO, listed amineptine under Schedule II of the Convention on Psychotropic Substances of 1971 (1971 Convention), due to its pharmacological similarities to psychomotor stimulants in schedule II and its dependence and abuse potential[2]. Additionally, WHO and the UN/CND considered studies demonstrating the ability of amineptine to cause hepatotoxicity, pancreatic injury and severe acne eruption. The United States is a signatory to this international treaty and is placing appropriate controls on amineptine by scheduling it under the CSA.

Pursuant to 21 U.S.C. 811(b), upon gathering the necessary data, on August 12, 2008 the Drug Enforcement Administration (DEA) requested from HHS a scientific and medical evaluation and scheduling recommendation for amineptine. On November 8, 2011, HHS provided to DEA a scientific and medical evaluation entitled "Basis for the Recommendation for Control of Amineptine in Schedule I of the Controlled Substances Act (CSA)" and a scheduling recommendation (HHS review, 2011[3]) [1]. Following consideration of the eight factors, HHS recommended that amineptine be controlled in schedule I of the CSA under 21 U.S.C. 812 (b).

The CSA requires DEA to determine whether the HHS' scientific and medical evaluation and scheduling recommendation along with other relevant data constitute substantial evidence of potential for abuse such as to warrant control [21 U.S.C. 811(b)]. This document contains an explanation of the relevant data that DEA considered. Pursuant to 21 U.S.C. 811(c), the Attorney General reviews the facts and all other relevant data. This document includes a summarized review of the relevant data and law enforcement

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[1] See HHS Notice titled "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Amfepramone (diethylproprion); Amineptine; Buprenorphine; Delta-9-tetrahydrocannabinol (dronabinol); Tramadol," published in the Federal Register on April 9, 2002 at 67 FR 17074, and HHS Notice titled "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendation for Amineptine (7-[10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)amino]heptanoic acid)," published in the Federal Register on February 3, 2003 at 68 FR 5295.

[2] The current "List of Psychotropic Substances Under International Control," also known as the "Green List," can be found on the website of the International Narcotics Control Board at www.incb.org/documents/Psychotropics/green_lists/Green_list_ENG_2010_53991_with_logo.pdf.

[3] Department of Health and Human Services Review: Basis for the Recommendation for Control of Amineptine in Schedule I of the Controlled Substances Act (CSA), 2011.

information as well as a determination to place amineptine into schedule I of the CSA. The information contained in this document is organized according to the eight factors as specified in 21 U.S.C. 811 (c).

Factor 1: Amineptine's Actual or Relative Potential for Abuse

In addition to the information HHS provided in its scientific and medical evaluation document for amineptine [1], DEA considers all other relevant data regarding amineptine's actual or relative potential for abuse. The term "abuse" is not defined in the CSA, however, the legislative history of the CSA suggests the following in determining whether a particular drug or substance has a potential for abuse[4]:

a. *Individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or*

b. *There is a significant diversion of the drug or other substance from legitimate drug channels; or*

c. *Individuals are taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs; or*

d. *The drug is so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may 2be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.*

HHS has evaluated the available abuse data on amineptine including animal and human data available in published scientific and medical journals, and the Critical Review Document on amineptine prepared by the WHO [2]. Reported findings from HHS include:

a. *Individuals are taking amineptine in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.*

As shown in the WHO [2] report, there is strong evidence of abuse of amineptine in Europe and Asia, where amineptine has been approved for use as an antidepressant. Case reports from various countries [3-13] (none in the United States due to its lack of Food and Drug Administration approval for marketing) have reported hospitalizations due to amineptine abuse and overdose. Amineptine has also been observed being abused in

[4] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No 91-1444, 91st Cong., Sess.1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603

combination with other drugs and alcohol, in addition to abuse due to its psychostimulant effects [3, 4, 14].

b. There is a significant diversion of amineptine from legitimate drug channels.

According to HHS, amineptine is not an approved human or veterinary drug product in the United States and has no known therapeutic application; therefore, it is not available through legitimate drug channels for medical purposes in the United States. There is no evidence of amineptine diversion or trafficking in the United States. In Europe and Asia, legitimate prescriptions, prescription theft or fraudulent prescriptions appear to be the drug source for majority of the amineptine abusers. Amineptine is diverted from legitimate channels, and taken without medical advice, thus creating a hazard to the health of the user. There is strong evidence that in humans and animals amineptine produces behavioral effects that are similar to those of schedule II stimulants such as amphetamine and cocaine. Thus it is reasonable to assume that amineptine has a substantial capability to be a hazard to the health of the user and to the safety of the community.

c. Individuals are taking amineptine on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs.

After first becoming available as an antidepressant pharmaceutical product in France in 1978, amineptine has been marketed subsequently in 66 countries throughout Europe, Africa, Asia and South America to treat depression. Abuse of amineptine for its stimulant effects resulted in case reports demonstrating escalation of the prescribed daily dose of 100-200 mg to 2000-4300 mg [3, 9, 10] and even 12 g daily [7] resulting in severe dependence. Various reporting centers including the Regional Centers of Pharmacovigilance and the Laboratory Eutherapie in France [14], the Observation of Illegal Drugs and Misuse of Psychotropic Medications in France [15], the WHO Collaborating Centre for international Drug Monitoring (also known as the Uppsala Monitoring Center) [16], and the WHO Critical Review [2] have reported a large number of case reports describing abuse and dependence associated with amineptine in numerous countries.

d. Amineptine is so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

While amineptine is a tricyclic antidepressant, it has a quicker onset of action than most other drugs in its class. Amineptine increases DA levels by inducing the synaptosomal release and inhibition of DA re-uptake, and to a lesser extent, increases NE levels, a mode of action mechanistically similar to the known central nervous system (CNS) stimulants amphetamine (schedule II) and cocaine (schedule II). The positive

reinforcing effects of amineptine were demonstrated in a self-administration study [17], which showed a higher frequency of self-administration of amineptine compared to saline. Amineptine has been shown to produce stimulant effects in the form of significantly increased motor activity in locomotor tests [18-23]. Additionally, a number of studies showed that amineptine increases extracellular DA levels in the brain, in particular, in the striatum and nucleus accumbens, structures constituting the reward pathway and known to be involved in abuse of drugs, including amphetamine and cocaine [22, 24-30]. These data suggest that amineptine is similar to psychostimulant drugs, such as amphetamine and cocaine with regard to their target neural circuits and their positive reinforcing properties.

In summary, the above data indicate that amineptine has the potential for abuse similar to other schedule II central nervous system stimulants such as cocaine and amphetamine.

Factor 2: Scientific Evidence of Amineptine's Pharmacological Effects

Amineptine, acting through a similar mechanism of action as amphetamine and cocaine (both in schedule II), elicits behavioral effects through its potentiation of monoaminergic transmission via action on DA and NE transporters which can result in euphoria, pyschostimulation, and suppression of fatigue and appetite.

Neurochemistry of Amineptine

According to the HHS review, amineptine is a DA re-uptake inhibitor and induces DA release and to a lesser extent it may also inhibit NE uptake and/or increase NE release. However, unlike other antidepressants such as serotonin reuptake inhibitors and some other tricyclic antidepressants, amineptine does not increase the extracellular levels of serotonin (5-HT).

Receptor and Neurotransmitter Studies

As mentioned in the HHS review document, amineptine produces its primary effect through inhibition of DA reuptake and increased release of DA as shown via *in vitro* and *in vivo* studies [22, 24-27, 29-31]. In particular, amineptine was shown to increase DA metabolite levels significantly in the striatum and limbic areas (nucleus accumbens and tuberculum olfactorium) [26, 27, 29, 31]. Studies also found that amineptine inhibits NE uptake and/or increases NE release, although to a lesser extent than DA [22, 25, 27], although these results were not confirmed by Dankova et al. [31] or Samanin et al. [23].

Animal Behavioral Effects

Animal behavioral studies have shown that amineptine has CNS activity, including anti-depressant, locomotor and anti-narcoleptic effects.

Anti-depressant Effect

According to the HHS review, several animal studies have demonstrated the anti-depressant effects of amineptine [32-35].

Borsini et al. [33, 34] demonstrated a significant dose-dependent reduction in immobility using the forced swim test in male rats following administration of amineptine. Following administration of the DA1/DA2 receptor antagonist haloperidol or the DA2 receptor antagonist sulpiride, the decrease in immobility was reversed, suggesting that DA is involved in the anti-immobility effect of repeated amineptine treatments in rats. A supporting study conducted in male mice also demonstrated a significant dose-dependent decrease in immobility via the tail suspension test following administration of amineptine [35]. In a subsequent experiment using reserpine-treated mice (reserpine is an indole alkaloid that depletes vesicular stores of DA, NE and 5-HT), amineptine had low efficacy in reducing immobility in the tail suspension test suggesting that DA plays a role in its anti-immobility effect.

Locomotor Effect

According to HHS, certain drugs that increase DA neurotransmission have been shown to stimulate motor activity in animals. Studies have also demonstrated a positive correlation between increased open-field locomotor activity and the reinforcing properties of drugs [36, 37]. In particular, several animal studies have demonstrated the locomotor stimulant effects of amineptine in a variety of animal species [18-23, 38].

Examples of the effects of amineptine include: 1) enhanced individual and social dynamic behavior in the adult male squirrel monkey [38]; 2) increased motor activity, sniffing and rearing equivalent to those produced by amphetamine at comparable doses in female rats [23]; 3) a significant dose-dependent increase in locomotor activity in an open field setting in male rats [20]; 4) an increase in locomotor activity in male mice [22]; and 5) a significant dose-dependent increase in horizontal and vertical motor activity in male mice [19].

Anti-narcoleptic Effect

According to the HHS review, amineptine significantly increased the wakefulness in a canine model of narcolepsy, although amineptine was less potent than amphetamine at increasing the time spent awake [39]. Amineptine was also shown to be associated with an arousal electroencephalogram pattern in rabbits [40].

Human Behavioral Studies

Anti-depressant Effect

According to the HHS review, various multi-center clinical studies have demonstrated the efficacy of amineptine as an antidepressant [41-46]. In addition, several clinical studies have compared the effectiveness and tolerability of amineptine with other antidepressants, including: amisupride [47]; amitriptyline [48]; clomipramine [49-51];

imipramine [52, 53]; fluoxetine [54, 55]; maprotiline [56]; minaprine [50]; moclobemide [57] and trimipramine [58]. These studies indicated that amineptine is as effective as other antidepressants, often with earlier onset of therapeutic effects. Ferreri [55] found fluoxetine, a selective serotonin reuptake inhibitor, to be more effective than amineptine in patients with a major depressive disorder, while Dalery et al. [54] showed that amineptine has efficacy similar to that of fluoxetine while supporting the earlier onset of therapeutic action.

In a large multi-center open label clinical trial investigating the effects of amineptine on patients diagnosed with a depressive disorder, physicians reported a positive outcome in over 75 percent of patients who were administered amineptine after seven days of treatment demonstrating an early onset of the antidepressant activity [44]. In a separate randomized, double-blind clinical trial comparing the efficacy of amineptine to imipramine in patients diagnosed with depressive disorders, patients receiving amineptine reported lower depression rating scale scores and the severity of illness was significantly decreased by day 28. Results demonstrated that amineptine had similar antidepressant activity and good tolerance as compared to imipramine, and had an earlier onset of therapeutic action of approximately seven days [52].

Effect on Sleep Cycle

As reported by HHS, studies have shown that amineptine affects sleep in healthy volunteers and in patients with depressive symptoms. One study demonstrated that amineptine significantly reduced the wakefulness time after the beginning of sleep as compared to placebo, and improved the subjective quality of sleep in addition to the subject's attention and concentration upon waking [59]. These effects were still evident after one week following the last administration. In a separate placebo controlled study, patients diagnosed with depressive syndrome had a significant improvement in depressive symptoms and had significantly increased the total number and duration of episodes of rapid eye movement sleep following administration of amineptine [60].

Factor 3: The State of Current Scientific Knowledge Regarding Amineptine

Chemistry

As stated in the HHS review document, amineptine is known as 7-[(10, 11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)amino]heptanoic acid. It is a white crystalline powder with a molecular weight of 337.5 (base) and 373.9 (hydrochloride salt) and a molecular formula of $C_{22}H_{27}NO_2$ (base) and $C_{22}H_{27}NO_2 \cdot HCl$ (hydrochloride salt). It is soluble in water and in methanol.

Clandestine Synthesis

As reported by HHS, according to the WHO critical review there are no reports of the clandestine manufacture or trafficking of amineptine [2]. Overall, the abuse appears to involve the pharmaceutical product. Since the publication of the WHO Critical Review

in 2002, a report describing the synthesis of amineptine was published [61]. This synthesis route produced an overall yield of 53 percent with a 99 percent HPLC purity. This synthetic procedure is available on the Internet.

Pharmacokinetics

The distribution, metabolism and excretion of amineptine have been studied in animals and humans [62-64]. In humans, orally administered amineptine is rapidly absorbed. Mean peak plasma concentrations of amineptine and its main metabolite occurred at 1 hour and 1.5 hours, respectively. Amineptine is metabolized in the liver and rapidly excreted and eliminated through the kidneys with mean half-lives of 0.8 hours for amineptine and 2.5 hours for the metabolite [62, 63, 85]. In humans, 70-75 percent of the administered dose of amineptine was excreted in the urine within 48 hours, with most of the elimination occurring within the first 12 hours [62].

Distribution of ^{14}C-amineptine was also evaluated using whole body autoradiography in the *Macaca fascicularis* monkey [64]. Results demonstrated high levels of radio-labeled amineptine in the liver and kidneys, with lower levels of activity in the blood, gastrointestinal tract and spleen. In brain radioactivity was observed in the cortex, putamen, caudate nucleus, globus pallidus, pulvinar and geniculate bodies, with lower levels noted in the hippocampus, substantia nigra and medulla.

Medical Use

As noted by HHS, amineptine has no approved medical use and no known therapeutic application in the United States. In 1978, amineptine was approved for use in France as an antidepressant [2] and subsequently marketed in 66 countries throughout Europe, Africa, Asia and South America. Initially manufactured by Servier in France as 100 mg tablets and capsules, a dose of 100-200 mg was administered in the majority of the clinical trials establishing the drug's efficacy as an anti-depressant [65]. Medical use of amineptine declined over the years, due to severe acne disruptions, hepatotoxicity and its potential for abuse and dependence. After being voluntarily discontinued in France and Spain by Servier in 1999 due to its abuse potential, amineptine was also withdrawn from the market in a various other countries due to its abuse and safety related problems [2].

While still produced in several developing countries, as of 2003, amineptine was withdrawn from the market in 49 of the 66 countries [16]. The status of current production of amineptine in other countries is not known, although a small quantity is most likely produced for research purposes.

Factor 4: Amineptine's History and Current Pattern of Abuse

As shown by HHS, there are numerous published reports of amineptine abuse including 186 cases of abuse between 1978 and 1988 as reported to the Regional Centers of Pharmacovigilance and the Laboratory Eutherapie in France, and 65 cases of abuse

between 1990 and 1998 in the Observation of Illegal Drugs and Misuse of Psychotropic Medications (OPPIDUM) database [14, 15].

At the 16th French Pharmacovigilance meeting [66] in November 1994, the Femand Widal Pharmacovigilance Centre reviewed 565 cases of amineptine "overconsumption" and reported multiple characteristics of amineptine abuse including: 1) amineptine abusers typically had a history of alcoholism, drug abuse and/or eating disorders; 2) 28 percent of the cases of amineptine abuse resulted in neuropsychiatric disorders; 3) 11 percent of patients developed acne-like lesions from amineptine use; 4) withdrawal from amineptine abuse was described as extremely difficult; 5) only 30 percent were abstinent after one month of withdrawal and long-term abstinence was uncommon and 6) most patients obtained amineptine from pharmacists by stealing or fraudulent prescriptions. Between 1980 and 1988, eight patients were treated at a hospital in France for amineptine abuse. The average daily intake of amineptine by these patients ranged from 1-2.5 g [4]. A repeated abuser in Spain presented to the hospital 14 times within a nine year period with amineptine-induced psychotic exacerbation. The last hospitalization of this patient occurred following consumption of up to 3 grams/day for five days and presented with symptoms of extreme psychomotor agitation, aggression, hallucinations, rapid speech and labile mood [12].

Trafficking

There are no reports of trafficking amineptine in the United States. Queries of DEA's System to Retrieve Information from Drug Evidence (STRIDE)/STARLiMS[5] and the National Forensic Laboratory Information System (NFLIS)[6] databases on November 17, 2020, did not generate any reports of amineptine, suggesting that it is not trafficked in the United States. In addition, the WHO Critical Review stated that there are no reports of amineptine trafficking outside the United States [2]. At the request of the DEA in April 2008 and again in September 2012, a query of the INTERPOL databases for updated law enforcement seizure information on amineptine resulted in no reports found.

Factor 5: The Scope, Duration, and Significance of Abuse of Amineptine

HHS reviewed the published case reports and other evidences of amineptine abuse and these findings are summarized below[1].

The majority of the reports of amineptine abuse involved patients who were prescribed amineptine for an affective disorder [3, 5, 8-10]. In these reports, abuse normally began one year after prescribing amineptine for the treatment of depression,

[5] STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from DEA, other federal agencies, and law enforcement agencies. On October 1, 2014, STARLiMS replaced STRIDE as DEA laboratory drug evidence data system of record.

[6] NFLIS is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories across the country. The NFLIS participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is over 97 percent. NFLIS includes drug chemistry results from completed analyses only.

especially in those with a history of alcoholism, intravenous drug abuse and eating disorders. Patients were known to independently increase their prescribed dosage over a period of weeks or months from 100-200 mg to 2000-4300 mg daily [3, 5, 8-11]. Amineptine abuse appears to be due to its psychostimulant effect. Other reasons cited for its abuse were increased energy, joy, work output, alertness and psychomotor performance [3-5, 7, 14]. As reported by the Center for Evaluation and Information on Pharmacodependence in southwest France, amineptine was one of the top 12 medications appearing in falsified prescriptions from December 1992 to November 1993 [67].

A query of the Internet in 2008, 2012 and April 2019 for amineptine identified several websites purporting to sell amineptine. The companies identified in the query were based outside the United States. The websites purported to sell a variety of pharmaceutical chemicals, but did not indicate the formulation (e.g. raw material or tablets), purity, price or quantity sold. In April 2011, and additional Internet query for amineptine identified at least two sites selling amineptine (Sunflower FZC [United Arab Emirates] and Shanghai HongDa Chemical Industry Co Ltd.) and various sites advertising amineptine for human use. The description of the manufacturing process of amineptine is also available on the internet (Merck Index 409, Kleeman & Engel p. 40, DOT 19 (I O) 547 (1983), I.N. p. 69 Melen, C., Danree, B. and Poignant, J.C.; US. Patent 3,758,528; September 11, 1973).

Amineptine is regulated by:

1. *International Control – World Health Organization (WHO) and United Nations*
   In 2003, the United Nations Commission on Narcotic Drugs, at the advice of the WHO, listed amineptine under Schedule II of the 1971 Convention on Psychotropic Substances.
2. *National Controls*
   Amineptine is controlled in Belgium, Canada, the Czech Republic, Denmark, Germany, Estonia, Greece, Italy, Latvia, Lithuania, Hungary, the Netherlands, Poland, Slovenia, Sweden and Norway (European Legal Database on Drugs, 2007).

Factor 6: What, If Any, Risk to the Public Health

According to the HHS review, there are no known fatalities resulting from amineptine use or abuse. Some of the main safety risks of amineptine are related to serious adverse effects, such as hepatotoxicity [68-70], acne [7, 71-76], and gastrointestinal (acute pancreatitis) effects [77]. In addition, neuropsychiatric symptoms including anxiety, insomnia, nervousness, irritability, dysarthria, acute psychosis, delusions, hallucinations, anorexia, agitation, psychotic disorders and confusion have resulted from abuse of amineptine [8-10, 66].

Two recent publications [83, 84] conducted queries of VigiBase™, the largest and most comprehensive pharmacovigilance database in the world. VigiBase™ is a collection of adverse drug reactions monitored by the Uppsala Monitoring Centre in Sweden.

Results demonstrated that from 1968-2014 (May 2014), 58.5% of all adverse drug reported for amineptine were associated with hepatotoxicity.

Factor 7: Amineptine's Psychic or Physiological Dependence Liability

As demonstrated in the HHS review [1], amineptine has been shown to produce physical and psychological dependence as supported by clinical evidence. While amineptine has no clearly defined withdrawal syndrome, there are reports of withdrawal symptoms including anxiety, dysphoria, nausea, brief psychotic episodes, tremor, psychomotor agitation, somatic symptoms and sleep disturbances [3-5, 9, 11, 13]. In addition, a strong desire to take amineptine was noted in individuals upon withdrawal of drug, a typical characteristic of psychological dependence [3-5, 8, 10, 12, 13].

Several studies have reported psychological (or "psychic") dependence associated with amineptine abuse. Berstschy et al. [4] documented "psychic dependence" in eight cases from a drug treatment center in France. The authors noted that there was a compulsive need to use the drug on a periodic (two cases) or continuing (six cases) basis in order to experience its psychomotor stimulant like effects. In one study, the three patients met the DSM-III-R criteria for substance abuse [9]. In another study, the two patients, who were taking up to 2 g daily upon admittance to the hospital, met the DSM-III-R criteria for psychoactive substance dependence [78]. Another patient's pattern of amineptine use also met the DMS-III-R diagnostic criteria for substance dependence [79]. The same patient reported a compulsive need to use the drug on a continuing basis. Another patient, who was abusing both amineptine and the benzodiazepine midazolam, exhibited tolerance to the drug, a craving for the drug, a decline in occupational functioning, and relapse [80]. There were also several cases in which the patients were unable to stop abusing amineptine after being admitted for treatment [8, 78, 81]. In two cases, patients left the treatment program early against medical advice [8, 78]. In another study of patients attending an out-patient clinic at drug addiction treatment centers in Kuwait, 127 out of 173 patients (73 percent) taking amineptine for more than a year were unable to discontinue their intake of amineptine upon request indicating a persistent desire factor [82].

Factor 8: Whether Amineptine Is an Immediate Precursor of a Substance Already Controlled

Amineptine is not an immediate precursor of any controlled substance of the CSA as defined by 21 U.S.C 802(23).

FINDINGS

Title 21, U.S.C. 812(b)(1) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for placement in schedule I of the CSA as a controlled substance. After consideration of the above eight factors determinative of control of a substance (21 U.S.C. 811(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by the HHS in concurrence with the National Institute on Drug Abuse, DEA finds that amineptine meets the following criteria for placement in schedule I of the CSA, under 21 U.S.C. 812 (b)(1).

1) Amineptine has a high potential for abuse.

The collected information suggests that amineptine meets the criteria and indicators set forth in the legislative history of the CSA for having abuse potential. Amineptine has stimulant and euphoric effects similar to amphetamine (C-II) and cocaine (C-II). It has a high potential for abuse that is equivalent to these drugs and has been abused in many countries in Europe and Asia where available, as described in sections 1, 4, 5 and 7.

2) Amineptine has no currently accepted medical use in treatment in the United States.

There are no approved New Drug Applications for amineptine nor is there a known therapeutic application for amineptine in the United States. Therefore, amineptine has no currently accepted medical use in treatment in the United States.

3) There is a lack of accepted safety for use of amineptine under medical supervision.

Clinical experience with amineptine as an antidepressant drug in other countries indicated that some patients misused and abused amineptine by stealing or falsifying prescriptions and taking doses 10 to 20 times higher than prescribed, resulting in serious hepatic, gastrointestinal, cardiovascular and psychiatric side effects necessitating hospitalization. Amineptine was once marketed in 66 countries within Europe, Africa, Asia and South America, but subsequently withdrawn from most of these countries due to lack of safety. Therefore, amineptine lacks the accepted safety for use under medical supervision.

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