U.S. Department of Justice

Drug Enforcement Administration

Schedules of Controlled Substances: Placement of Alfaxalone into Schedule IV
Background, Data, and Analysis:
Eight Factors Determinative of Control and
Findings Pursuant to 21 U.S.C. 812(b)

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I. Background

Alfaxalone (5α-pregnan-3α-ol-11,20-dione, previously spelled as alphaxalone), a substance with central nervous system (CNS) depressant properties, is a neurosteroid that is a derivative of 11-alpha-hydroxy-progesterone. A New Animal Drug Application (NADA) for alfaxalone, as an intravenous injectable anesthetic was recently approved by the Food and Drug Administration (FDA) for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance of anesthesia with an inhalant anesthetic in cats and dogs.

According to the scientific and medical evaluation conducted by the Department of Health and Human Services (HHS), alfaxalone primarily acts as an agonist at the gamma-aminobutyric acid (GABA) receptor-channel complex, with a mechanism of action at this site similar to that of barbiturates like phenobarbital (Schedule IV) and methohexital (Schedule IV), benzodiazepines such as diazepam (Schedule IV) and midazolam (Schedule IV), as well as the anesthetic agents, propofol (Schedule IVunder consideration) and fospropofol (Schedule IV). Alfaxalone has abuse potential similar to that of other sedatives with similar modes of action and effects such as midazolam (Schedule IV), chlordiazepoxide (Schedule IV), and a similar indication to fospropofol (Schedule IV) and propofol (Schedule IV under consideration).

According to HHS, in 1972, pharmaceutical products containing alfaxalone were approved as anesthetics for use in humans (Althesin®) and in animals (Saffan®) in several countries including Australia, Canada, France, Italy, New Zealand, Spain and the United Kingdom (U.K.). These older products were different from the recently approved formulation for use in the U.S. with regard to their formulation characteristics. These older products contained solvent Cremophor-EL, a castor oil derivative, to aid in solubilizing alfaxalone in saline. Additionally, these older products contained alfadalone, a closely related neurosteroid, to further enhance the solubilixation of alfaxalone. During the clinical use of Althesin®, adverse events ascribed to Cremophor-EL associated release of histamine or histamine-like substances were observed. This resulted in the withdrawal of Althesin® from human use in 1984. However, an alfaxalone-containing veterinary product, Saffan® is continuing to be used in some countries for cats and primates. The recently approved veterinary product contains a single alfaxalone (10 mg/ml) solubilized in 2-hydroxypropyl-beta-cyclodextrin (2-HPCD) and water with a phosphate buffer solution. The same formulation is currently marketed for use as an anesthetic in cats and dogs in Australia and New Zealand (in 2000), South Africa (2005), U.K. (2006), Germany, France, Ireland, Belgium, Netherlands, Spain (2008) and Canada (2009).

On July 17, 2012, the Department of Human Health Service (HHS) provided to the Drug Enforcement Administration (DEA) a scientific and medical evaluation entitled "Basis for the Recommendation to Control of Alfaxalone in Schedule IV of the Controlled Substances Act" and a scheduling recommendation. Following consideration of the eight factors determinative of control or removal from the schedules (21 U.S.C. 811(c)) and findings required for placement in a particular schedule (21 U.S.C. 812(b)), HHS recommended that alfaxalone be controlled in Schedule IV of the Controlled Substances Act (CSA).

The CSA requires DEA, as delegated by the Attorney General,[1] to determine whether HHS's scientific and medical evaluation and all other relevant data constitute substantial evidence of potential for abuse such that the substance should be scheduled (21 U.S.C. 811(b)).

[1] 28 CFR 0.100(b)

II. Eight Factors Determinative of Control

Pursuant to 21 U.S.C. 811(c), DEA must consider eight factors in making any finding of substantial evidence of potential for abuse, including the data and law enforcement information relevant thereto.

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

In addition to the information HHS provided in its scientific and medical evaluation document for alfaxalone, DEA considers all other relevant data regarding alfaxalone's actual or relative potential for abuse. Since alfaxalone is a new veterinary product and has not been marketed in the United States, information on actual abuse of alfaxalone in the United States is not available. However, the legislative history of the CSA suggests using the following criterion in determining whether a particular drug or substance has a potential for abuse:

> *The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, 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.*[2]

According to HHS, alfaxalone is thought to interact with the gamma-aminobutyric acid subtype A (GABA)-A receptors, and to enhance the activity of GABA, the principal inhibitory neurotransmitter in the central nervous system (CNS). Alfaxalone acts on the CNS and induces sedation and anesthesia. This pharmacological evidence suggests that the abuse potential of alfaxalone is comparable to other drugs with a similar mechanism of action, and similar anesthetic properties, such as midazolam (Schedule IV), methohexital (Schedule IV), fospropofol (Schedule IV) and propofol (Schedule IV under consideration). Midazolam, a rapid and short acting benzodiazepine, is used for preoperative sedation, anxiolysis and amnesia. Methohexital (Schedule IV), a rapid and ultra-short acting barbiturate, is used for intravenous induction of anesthesia prior to use of other general anesthetic agents, for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli, and as an agent for inducing hypnosis. Fospropofol (Schedule IV) is used for use in a manner similar to that of propofol (Schedule IV under consideration), in monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures. Propofol (Schedule IV under consideration) is approved for use in anesthesia in humans and animals. Similar to the above mentioned several Schedule IV sedative-hypnotics, alfaxalone acts as an inhibitor on the CNS. Thus, alfaxalone may produce the abuse potential similar to that of other Schedule IV sedative-hypnotics (HHS review, 2012).

The HHS review states that there are no reports of human abuse of alfaxalone in the scientific literature. Based on the similarities of their mechanisms of action and their intended routes of administration for clinical use of alfaxalone and propofol and the fact that 96% of

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[2] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4601.

propofol abuse reports involved abuse by medical professionals, HHS reasoned that alfaxalone abuse might be by medical professionals who have access to the drug and have knowledge in the intravenous administration of drugs (HHS review, 2012).

According to HHS, there are no published studies of abuse potential for alfaxalone in humans. However, there is evidence that alfaxalone produces sedative-hypnotic, midazolam-like discriminative stimulus effects in rats and monkeys, as well as some ethanol-like effects in rats. Based on the pharmacological similarities to other Schedule IV potent sedative-hypnotic drugs (such as midazolam, methohexital and fospropofol), the consequences of abuse of alfaxalone can be predicted to be similar to those drugs mentioned above. Furthermore, abuse and misuse of these drugs might result in death (HHS review, 2012). HHS review also concluded that the overt behavioral effects and adverse events produced by alfaxalone in animals are similar to those caused by Schedule IV benzodiazepines and barbiturates. Alfaxalone produces full generalization in animal drug discrimination studies to the Schedule IV benzodiazepine, midazolam (HHS review, 2012).

HHS stated that the relative abuse potential of alfaxalone can be considered no greater than the Schedule IV substances such as fospropfol, propofol, and midazolam and less than that of other sedatives in Schedule III and provided the following rationale for this conclusion:

1. Alfaxalone produces effects in animals that are similar to the effects produced by other sedative-hypnotic drugs, such as midazolam (Schedule IV), propofol (Schedule IV under consideration) and fospropofol (Schedule IV), making it likely that alfaxalone will have the same potential for abuse as those substances.
2. In view of the abuse patterns of propofol (Schedule IV under consideration), it is reasonable to assume that alfaxalone, similar to propofol, will be diverted from legitimate drug channels by medical professionals who have access to the drug and who are knowledgeable in the intravenous administration of drugs.
3. Alfaxalone might be abused for its sedative effects contrary to medical advice.
4. The potential of alfaxalone to create a hazard for the user is expected to be similar to that of other potent Schedule IV sedative-hypnotics.

In summary, alfaxalone has a mechanism of action that is similar to that of drugs in Schedule IV (benzodiazepines, barbiturates, propofol and fospropofol) and its abuse potential would be similar to these drugs.

Factor 2: Scientific Evidence of Alfaxalone's Pharmacological Effects

Neurochemical Effects of Alfaxalone

According to the HHS review, alfaxalone acts on GABA-A receptors, enhancing the function of the GABA-A receptor. The GABA-A receptor is the site of action of GABA, which is considered the principal inhibitory neurotransmitter in the CNS. The GABA-A receptor is a ligand-gated chloride channel consisting of five subunits and a central chloride channel. GABA-A receptors contain at least one alpha, one beta and one gamma subunit and also there are several

types of subunits. Benzodiazepines and other GABA agonists favor the channel opening and the influx of chloride.

According to the HHS review, alfaxalone acts directly through the GABA-A receptor-channel complex and increases the probability that the channel will enter into naturally-occurring open states of relatively long duration (Cottrell et al., 1987; Twyman and MacDonald, 1992; Ueno et al., 1997; Siegwart et al., 2003). This activity is thought to be the result of enhancement of GABA-elicited chloride currents, as demonstrated by the ability of a GABA-A receptor antagonist, bicuculline to block chloride currents (Zhang and Jackson, 1994; Burg et al., 1998). The activity of alfaxalone on GABA receptors is similar to that of barbiturates like phenobarbital and methohexital (Schedule IV) as well as anesthetic agents like propofol (Schedule IV under consideration) and fospropofol (Schedule IV), a pro-drug that is rapidly converted to propofol (MacDonald and Olsen, 1994; Bai et al., 1999). Furthermore, similar to benzodiazepines such as diazepam and midazolam, alfaxalone can also increase the frequency of single channel openings (MacDonald and Olsen, 1994; Twyman and MacDonald, 1992). Additionally, alfaxalone has been shown to inhibit T-type calcium channels through a mechanism involving activity at nicotinic acetylcholine receptors (Shiraishi et al., 2002; Todorovic et al., 2004).

As stated in HHS review, *in vitro* receptor binding studies conducted by the Sponsor show that alfaxalone has a low affinity (~ 41- 48% of binding inhibition) at GABA-A receptor channels. In addition, alfaxalone does not significantly bind to major steroid nuclear receptors including androgens, estrogens, glucocorticoids or progesterone receptors (HHS review, 2012).

Alfaxalone does not affect cannabinoid (CB1 subtype), dopamine (D1, D2, D3, D4 and D5 subtype), glutamate (AMPA, kainate, and NMDA subtype), opioid (mu, kappa and delta subtype) and serotonin (1A, 2B, 2C, 3, 5A and 6 subtype) receptors, nor does it affect the transporters for dopamine, norepinephrine and serotonin.

The HHS review concludes that alfaxalone has the ability to enhance the function of the GABA-A receptor-associated channel, and consequently shares sedative, hypnotic and anesthetic properties with other drugs that act via the GABA-A receptor, such as benzodiazepines (Schedule IV) and barbiturates (Schedule II and III).

DEA further notes that, besides its effects on GABA-A receptors, a study using an *in vitro* Xenopus oocyte expression system reported that alphaxalone also inhibited the function of M-1 and M-3 muscarinic receptors, through a mechanism of partially interfering with the quinuclidinyl benzilate (QNB) binding sites on the receptors (Shiraishi et al., 2003). A role of alfaxalone for co-activating glycine receptors *in vitro* was also reported and reviewed by DEA (Weir et al., 2004; Ahrens et al., 2008).

Pre-clinical Behavioral Studies

According to the HHS review, similar to chlordiazepoxide (Schedule IV), alfaxalone has been shown to produce anxiolytic-like behavioral effects in rat models of anxiety, such as the elevated plus maze, the conflict test and restraint stress (Britton et al., 1991; Heinrichs et al., 1994).

The drug discrimination paradigm is widely accepted as an animal model to predict human subjective effects. This procedure provides a direct measure of stimulus specificity of a test drug in comparison with a known standard drug, or a neutral stimulus (e.g. injection of saline water). In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, it is highly likely that this new drug will produce pharmacological effects (including subjective effects) in humans similar to the known drug of abuse and would be similarly abused by humans (Balster and Bigelow, 2003; Panlilio and Goldberg, 2007). In an HHS-cited published drug discrimination study, in which rats were trained to discriminate midazolam (Schedule IV) from saline, alfaxalone fully generalized to the midazolam discriminative cue. The main rationale for selecting midazolam as the reference drug is that it is a representative Schedule IV benzodiazepine with known abuse-related properties and as similar to other benzodiazepines, alfaxalone is indicated for use as a pre-anesthetic/anesthetic medication (McMahon and France, 2006; HHS review, 2012). Both intravenous and oral administration of alfaxalone produced midazolam-like discriminative stimulus effects in rats. These results are consistent with previously published studies showing ethanol-like discriminative stimulus effects of alfaxalone and with other studies showing that other neurosteroids have barbiturate-like or benzodiazepine-like discriminative stimulus effects in rats and monkeys. This pharmacological profile of alfaxalone is consistent with neurosteroids with GABAergic effects (HHS review, 2012).

According to the HHS review, the oral administration of alfaxalone as compared to its intravenous administration is 100 times less potent for producing midazolam-like effects. Alfaxalone has a low oral bioavailability (about 2%). It has been shown that an intravenous dose of about 50 mg of alfaxalone results in anesthesia in humans with a plasma level of 3 mg/L. Accordingly, an oral dose of about 2500 mg might be expected to result in anesthesia at the plasma level of 3 mg/L in humans, and thus oral doses of 250 to 800 mg of alfaxalone should be needed to produce a sub-anesthetic intoxication at plasma levels in a range of 0.3 to 1.0 mg/L. For a vial containing 100 mg of alfaxalone for an oral use, an amount of 2.5 to 8 vials would be needed to produce a "high". However, the diluted and less concentrated dosage form may reduce the attractiveness of the veterinary formulation of alfaxalone as a drug of abuse (Simpson, 1978; Sear and Sanders, 1984; HHS review, 2012).

Self-administration studies in which animals are trained to press a lever in order to receive an injection of a drug are an extremely valuable tool to evaluate the abuse potential of a novel drug or other substances. These studies test the reinforcing effects of an abusable drug. Nearly all of the drugs that maintain self-administration in animals are also abused by humans. The most commonly used method for determining whether a novel substance will be self-administered by an animal is substitution of a novel substance from a self-administration baseline. In this procedure, animals (rhesus monkeys, baboons or rats) are trained to lever-press for infusions of a known drug or substance of abuse. After responding has stabilized, the substance of interest is substituted for the training drug. If responding over time decreases to levels similar to those when saline is substituted for the training drug, the novel substance is not serving as a reinforcer and hence is unlikely to have an abuse potential similar to that of the training drug. As stated in the HHS review, self-administration studies in animals with pregnanolone, allopregnanolone, endogenous metabolites of progesterone and a neuroactive

steroid, Co 8-7071, showed that these substances produce some positive reinforcing effects in rats and rhesus monkeys (HHS review, 2012). These substances, similar to alfaxalone, positively modulate GABA-A receptors by binding at the neurosteroid modulatory site. The HHS review stated that these data are predictive of abuse potential of alfaxalone. In addition, the HHS review also cited recent evidence that alpha4, beta3 and delta GABA-A receptors are modulated by both THDOC, a neurosteroid, and propofol. Based on this potential overlap in cellular targets, comparable kinetic profiles, and similar clinical indications for propofol and alfaxalone, HHS reasoned that alfaxalone may produce reinforcing effects similar to those of propofol. HHS also stated that propofol has been reported to produce reinforcing effects in rats and baboons (HHS review, 2012).

In summary, alfaxalone, similar to chlordiazepoxide (Schedule IV), has anxiolytic activity in animals. Intravenous and oral administration of alfaxalone produced midazolam-like (Schedule IV) discriminative stimulus effects in rats, and it may share propofol's reinforcing effects. The abuse-related neuropharmacology profile of alfaxalone is similar to those Schedule IV substances.

Factor 3: The State of Current Scientific Knowledge Regarding Alfaxalone

As stated in the HHS review document, the chemical name of alfaxalone is 5α-pregnan-3α-ol-11, 20-dione. It is a derivative of 11-alpha-hydroxy-progesterone and thus has a chemical structure very similar to the steroid, progesterone. Alfaxalone has a molecular formula of $C_{21}H_{32}O_3$ and a molecular weight of 332.5 g/mol, and a melting point of 165° to 171°C. The Chemical Abstract Registry number (CAS #) is 23930-19-0. Alfaxalone is sparingly soluble in water (< 5 μg/ml), which may limit its abuse via intravenous routes. However, complexation with cyclodextrins, especially 2-hydroxypropyl-beta-cyclodextrin (2HPCD) increases the water solubility of alfaxalone to 80 mg/ml (Brewster et al., 1989). According to the HHS review, the alfaxalone product for veterinary anesthesia will be formulated as a 10 mg/ml solution of alfaxalone in 2HPCD (80 mg/ml), sodium phosphate buffer and water, adjusted to a pH of 6.5 to 7. According to the Sponsor's information cited by the HHS review, the synthesis and purification of alfaxalone and its intermediary chemicals are highly complex processes, and thus, it is likely that its manufacture requires expertise in chemistry manufacture (HHS review, 2012).

The HHS review cited information provided by the Sponsor regarding pharmacokinetic studies conducted in laboratory animals such as rats, cats, dogs. The half-lives of alfaxalone are 24-37 and 45-77 minutes in dogs and cats, respectively. The clearance of alfaxalone is 59 ml/min/kg in dogs and 28 ml/min/kg in cats and the primary routes of elimination in the rat are biliary (65%) and renal (35%) routes. The half-life of alfaxalone in humans is about 35 minutes. The major metabolites in humans are glucuronidated and the primary route of elimination is through renal (80%). Oral bioavailability of alfaxalone is about 2% as compared to its intravenous administration in humans. In a clinical study cited by the HHS review, an intravenous administration of 50 mg alfaxalone produced plasma levels of about 3 mg/L, accompanied by anesthesia in humans (Sear and Sanders, 1984). A veterinary product that is recently approved by the FDA contains 100 mg of alfaxalone per vial (a 10 ml vial of formulated solution, 10 mg/ml of alfaxalone) which would be sufficient to produce anesthesia in two

individuals when administered intravenously. Further, HHS states that because, anesthetics such as alfaxalone can be abused at subanesthetic doses, a 100 mg vial of alfaxalone drug product administered intravenously could be used repeatedly by the same individual, or by multiple individuals, who intended to abuse the substance (HHS review, 2012).

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

As stated in the HHS review, the information on alfaxalone's history and current pattern of abuse is provided by the Sponsor. Those information sources included (1) the medical literature for abuse case reports, (2) a search of Internet sites including Erowid (www.erowid.org), Streetdrugs.org (www.streetdrugs.org), Lyaceum forum (www.lycaeum.org) and Drugs-forum (www.dmgs-fomm.com) for evidence of alfaxalone abuse and (3) a search result from poison control centers. Because alfaxalone has been marketed in the U.K. since 2007, the Sponsor submitted to HHS the results of a search of pharmacovigilance reports to the UK Veterinary Medicines Directorate. None of the above sources contained evidence of abuse of alfaxalone by humans. According to the HHS review, a search of the publically-available pharmacovigilance database provided by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) website conducted by the Sponsor also did not produce reports related to alfaxalone abuse.

DEA conducted a search of several major national drug abuse monitoring programs including the Drug Abuse Warning Network (DAWN), the National Poison Data System from American Association of Poison Control Centers (AAPCC), DEA's National Forensic Laboratory Information System (NFLIS) and the System to Retrieve Information from Drug Evidence (STRIDE), and the National Survey on Drug Use and Health (NSDUH) operated by Substance Abuse and Mental Health Services Administration (SAMHSA). None of the drug abuse databases above present any result associated with alfaxalone abuse. It may be due to the fact that alfaxalone-containing products have not been marketed in the United States to date.

However, alfaxalone's pharmacological properties suggest that its pattern of abuse would be similar to other drugs used in maintenance and induction of anesthesia, such as midazolam (Schedule IV) and propofol (Schedule IV under consideration).

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

As mentioned above in Factor 4, a comprehensive search by DEA of the major national drug abuse monitoring programs found no evidence of human abuse of alfaxalone in the U.S.

However, as stated in the HHS review, the Sponsor proposed a post-marketing surveillance program. The Sponsor and the U.S. distributor of alfaxalone will utilize the "suspicious order monitor system" to monitor the diversion of this product. This system evaluates order quantities, buying patterns, and customer class regarding orders of unusual volume that could indicate diversion. As part of their monitoring, the U.S. distributor also searches daily the DEA website for new abuse issues and for the abuse-related data from HHS's Substance Abuse and Mental

Health Administration Services (SAMHSA). Additionally, the Sponsor will provide FDA with pharmacovigilance information for both animal and human adverse events from all markets.

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

According to HHS, the abuse of alfaxalone is likely to pose a similar risk to public health as that of Schedule IV sedative hypnotics and CNS depressants such as midazolam and methohexital, and anesthetic propofol (Schedule IV under consideration).

According to the HHS review, the public health risks of alfaxalone are mostly risks to the individual abuser. Abuse of alfaxalone may lead to death of the abuser or other adverse events that affect behavior, reaction ability and timing in operating a motor vehicle or machinery. As an anesthetic, the adverse events (AEs) that are likely to result from alfaxalone use are usually similar to those arising from the use of most general anesthetics. These events include apnea, bradycardia, bradypnea, hypertension, hypotension, hypothermia, hypoxia, unacceptable anesthesia quality, tachycardia and emesis. These AEs were found in animal studies involving cats and dogs (HHS review, 2012). Alfaxalone, as anesthetic product if used in excess, carries potential for overdose. HHS cited two cases involving the accidental overdose of the alfaxalone human product, Althesin®, a human product containing combination of alfaxalone/alfadolone which was previously withdrawn from market. But, the two patients survived with the medical aid of positive pressure ventilation (HHS review, 2012).

According to the HHS review, the occurrence of an accidental or purposeful overdose of Alfaxan®, containing 10 mg/ml of alfaxalone is unlikely. HHS reasoned that if a person were trying to duplicate the same accidental overdose of alfaxalone as described above through an intravenous injection route, he or she would be required to draw up in a syringe more than 300 mg of alfaxalone, meaning large volumes of Alfaxan®. The self-administration of these large volumes of Alfaxan® through intravenous injection would be a very difficult if not impossible to perform, as the person would likely become anesthetized after the first 4.2 ml of the injection. If a person were to drink Alfaxan® to try to cause overdose, it would require 100 times more of the drug because of alfaxalone's poor oral bioavailability (1 - 2%) versus the intravenous route of administration. The HHS review further states that alfaxalone, similar to propofol, might be used for a criminal purpose. HHS cited a recently published case report describing that a registered male nurse in an intensive surgical care unit used propofol to murder one of his acquaintances (HHS review, 2012).

The HHS review stated that currently, alfaxalone is not known to be associated with any other systemic toxicity. Alfaxalone solution has been comprehensively investigated for safety and efficacy within the target animal species. In an efficacy study cited by the HHS review, 207 and 182 client-owned dogs and cats, respectively, were successfully anesthetized with clinically recommended dosages of alfaxalone for various surgical procedures. All dogs and cats survived their respective studies and were discharged from medical facilities on the same day. Due to its short-term use as an anesthetic in veterinary hospitals, little is known about other health effects that might occur in someone abusing the drug chronically (HHS review, 2012).

In summary, the available data indicates that abuse of alfaxalone may present risks to the public health at a level similar to those associated with the abuse of other sedative hypnotics and CNS depressants, such as midazolam and methohexital which are controlled in Schedule IV of the CSA and propofol (Schedule IV under consideration). The major adverse events of these anesthetics include respiratory depression and deaths.

Factor 7: Alfaxalone's Psychic or Physiological Dependence Liability

The HHS review states that studies of abrupt discontinuation of alfaxalone were not conducted. However, a study (McMohan et al., 2007) cited by the HHS review suggested the ability of alfaxalone to produce physical dependence. McMahon and his associates found that alfaxalone administration, as well as pregnanolone reduced the discriminative cue produced by flumazenil-precipitated withdrawal following chronic administration of benzodiazepines such as diazepam or lorazepam (both Schedule IV) in Rhesus monkeys (McMahon et al., 2007). However, unlike benzodiazepines, alfaxalone and other progesterone-derived neurosteroids produced this effect at doses that failed to produce midazolam-like discriminative stimulus effects. Hence, this generalization to a cue associated with benzodiazepine withdrawal may be due to the ability of alfaxalone to suppress symptoms of benzodiazepine withdrawal rather than true cross dependence (McMahon et al., 2007). The HHS review concludes that alfaxalone and pregnanolone can decrease withdrawal resulting from chronic administration of other positive GABA-A receptor modulators (HHS review, 2012).

According to HHS, there is no data available on the effects of abrupt discontinuation of alfaxalone because, as an anesthetic, it is not used chronically and not available for chronic use.

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

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

III. Findings for Schedule Placement Pursuant to 21 U.S.C. 812(b)

21 U.S.C. 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, safety for use under medical supervision, and physical or psychological dependence for scheduling under 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 HHS, DEA finds that alfaxalone meets the following criteria for placement in Schedule IV of the CSA pursuant to 21 U.S.C. 812 (b)(4).

1) Alfaxalone has a low potential for abuse relative to the drugs or other substances in Schedule III.

The information presented suggests that the abuse potential of alfaxalone is less than that of Schedule III drugs and is similar to that of Schedule IV drugs such as phenobarbital (Schedule IV) and methohexital (Schedule IV), as well as anesthetics such as propofol (Schedule IV under consideration) and fospropofol (Schedule IV). The mechanism of action of alfaxalone at the GABA receptor-channel complex is similar to that of some schedule IV benzodiazepines (diazepam and midazolam), barbiturate drugs (phenobarbital and methohexital), as well as the anesthetics, propofol (Schedule IV under consideration) and fospropofol (Schedule IV). Furthermore, anxiolytic and discriminative stimulus effects of alfaxalone are similar to those produced by midazolam (Schedule IV) and chlordiazepoxide (Schedule IV). Thus, alfaxalone has a low potential for abuse relative to the drugs or other substances in Schedule III.

2) Alfaxalone has a currently accepted medical use in the United States.

Alfaxalone was approved by FDA as a veterinary anesthetic product for the induction and maintenance of anesthesia and for induction of anesthesia followed by maintenance of anesthesia with an inhalant anesthetic in cats and dogs. Thus, alfaxalone has a currently accepted medical use in the United States.

3) Abuse of alfaxalone may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Alfaxalone may produce limited physical and psychological dependence relative to drugs in Schedule III. Alfaxalone has been shown to inhibit the discriminative cue produced by flumazenil-precipitated withdrawal, following chronic administration of Schedule IV benzodiazepines (diazepam or lorazepam) in monkeys. This study suggests that alfaxalone can suppress withdrawal resulting from chronic administration of other positive GABA-A receptor modulators and therefore, it may have the potential to produce dependence. Thus, abuse of alfaxalone may lead to limited physical dependence relative to the drugs or other substances in Schedule III.

References

1. Department of Health and Human Services (HHS) Review: Basis for the Recommendation to Control Alfaxalone in Schedule IV of the Controlled Substances Act. 2012.

2. Ahrens J, Leuwer M, Demir R, Krampfl K, Foadi N, Haeseler G. The anesthetic steroid alphaxalone positively modulates alpha1-glycine receptor function. Pharmacology. 2008; 82: 28-32.

3. Bai D, Pennefather PS, MacDonald JF, Orser BA. The general anesthetic propofol slows deactivation and desensitization of GABAA receptors. J. Neurosci. 1999, 19:10635- 46.

4. Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug and Alcohol Dependence, 2003; 70: S13-40.

5. Britton KT, Page M, Baldwin H, Koob GF. Anxiolytic activity of steroid anesthetic alphaxalone. J Pharmacol Exp Ther. 1991; 258:124-9.

6. Brewster ME, Estes KS, Bodor N. Development of a non-surfactant formulation for alfaxalone through the use of chemically-modified cyclodextrins. J Parenter Sci Technol. 1989; 43:262-5

7. Burg M, Heinemann U, Schmitz D. Neuroactive steroids induce GABAA receptor-mediated depolarizing postsynaptic potentials in hippocampal CA1 pyramidal cells of the rat. Eur J Neurosci. 1998; 10:2880-6.

8. Cottrell GA, Lambert JJ, Peters JA. Modulation of GABAA receptor activity by alphaxalone. Br J Pharmacol. 1987; 90:491-500.

9. Heinrichs SC, Menzaghi F, Pich EM, Baldwin HA, Rassnick S, Britton KT, Koob GF. Anti-stress action of a corticotropin-releasing factor antagonist on behavioral reactivity to stressors of varying type and intensity. Neuropsychopharmacology. 1994; 11:179-86.

10. Macdonald RL, Olsen RW. GABAA receptor channels. Annu Rev Neurosci. 1994; 17:569-602.

11. McMahon LR, France CP. Combined discriminative stimulus effects of midazolam with other positive GABAA modulators and GABAA receptor agonists in rhesus monkeys. Psychopharmacology (Berl). 2005; 178:400-9.

12. Panlilio LV, Goldberg SR. Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction. 2007; 102: 1863-70.

13. Sear JW, Sanders RS. Intra-patient comparison of the kinetics of alphaxalone and alphadolone in man. Eur J Anaesthesiol. 1984; 1:113-22.

14. Shiraishi M, Minami K, Shibuya I, Uezono Y, Ogata J, Okamoto T, Murasaki O, Kaibara M, Ueta Y, Shigematsu A. The inhibitory effects of alphaxalone on M1 and M3 muscarinic receptors expressed in Xenopus oocytes. Anesth Analg. 2003; 97:449-55.

15. Shiraishi M, Shibuya I, Minami K, Uezono Y, Okamoto T, Yanagihara N, Ueno S, Ueta Y, Shigematsu A. A neurosteroid anesthetic, alphaxalone, inhibits nicotinic acetylcholine receptors in cultured bovine adrenal chromaffin cells. Anesth Analg. 2002; 95:900-6.

16. Siegwart R, Krahenbuhl K, Lambert S, Rudolph U. Mutational analysis of molecular requirements for the actions of general anesthetics at the gamma-aminobutyric acid A receptor subtype, alpha1 beta2 gamma2. BMC Pharmacol. 2003; 12:3-13.

17. Simpson ME. Pharmacokinetics of Althesin - Comparison with lignocaine. Br J Anaesth. 1978; 50:1231-5.

18. Todorovic SM, Pathirathna S, Brimelow BC, Jagodic MM, Ko SH, Jiang X, Nilsson KR, Zorumski CF, Covey DF, Jevtovic-Todorovic V. 5beta-reduced neuroactive steroids are novel voltage-dependent blockers of T-type Ca2+ channels in rat sensory neurons in vitro and potent peripheral analgesics in vivo. Mol Pharmacol. 2004; 66:1223-35.

19. Twyman RE, Macdonald RL. Neurosteroid regulation of GABAA receptor single-channel kinetic properties of mouse spinal cord neurons in culture. J Physiol. 1992; 456:215-45.

20. Ueno S, Bracamontes J, Zorumski C, Weiss DS, Steinbach JH. Bicuculline and gabazine are allosteric inhibitors of channel opening of the GABAA receptor. J Neurosci. 1997; 17:625-34.

21. Weir CJ, Ling AT, Belelli D, Wildsmith JA, Peters JA, Lambert JJ. The interaction of anaesthetic steroids with recombinant glycine and GABAA receptors. Br J Anaesth. 2004; 92:704-11.

22. Zhang SJ, Jackson MB. Neuroactive steroids modulate GABAA receptors in peptidergic nerve terminals. J. Neuroendocrinol. 1994; 6:533-8.