Expert Committee on Drug Dependence

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World Health Organization

Expert Peer Review for Etizolam

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential: Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in $GABA_A$ receptors. It has pharmacologic resemblance to the benzodiazepines with mainly anxiolytic and less sedative effects due to its lower intrinsic activity at the a1 subtype of the alpha subunit ($GABA_A$ receptors).

Preclinical Studies

The critical review described a drug discrimination study in Rhesus monkeys indicating the dependence potential of etizolam. It was reported that etizolam fully substituted for pentobarbital and there was an associated rightward shift of the dose-response curve following pretreatment with flumazenil, a benzodiazepine antagonist.

Human Studies

In as much as the dependence potential of the benzodiazepines is well known, there are few case reports demonstrating the dependence potential of etizolam. Specifically, two case reports published in 2014 described etizolam dependence. One case report described a 23-year old man who was taking up to 2.5 mg per day of etizolam with inability to stop its use; withdrawal symptoms characteristic for benzodiazepine withdrawal (palpitations, impaired sleep, agitation, tremors) were recorded. The second case report involved a 22-year old woman using 5 mg or more of etizolam per day who was also unable to stop the medication by herself. Successful dose reduction (to 0.3 mg per week) of etizolam was recorded without withdrawal symptoms.

Abuse potential: The critical review did not demonstrate published abuse liability studies in animals. Although the review stated an increase in the reports of the abuse potential of etizolam in humans, the specified study was a case report of a 31-year-old man who presented to an Emergency Department of a hospital in the Unites States with features suggestive of drug overdose and a history of etizolam and other substance

abuse. Laboratory analysis confirmed the presence of codeine, high morphine levels and 6-acetyl morphine suggesting recent heroin use. Etizolam was also present. The publication described an annual increase in the number of etizolam-related cases of drug abuse from unpublished data from the American Association of Poison Control Centers in the United States of America from 2011 with 41 cases as of 2014.

b. Risks to individual and society because of misuse

The adverse effects of etizolam are similar to those produced by the benzodiazepines and include drowsiness and muscle weakness. Blepharospasm (sustained involuntary closing of the eyelids) and paradoxical excitation have also been reported. Etizolam misuse has been associated with several deaths. Although toxicology reports showed evidence of etizolam in these drug-related deaths, there was also laboratory evidence of multiple drug use in all of the cases described in the report. Opioids, alcohol and other psychoactive substances were also detected. Therefore, the toxicological effects of etizolam alone were difficult to determine. Studies indicate that the median lethal dose (LD_{50}) of etizolam is higher (that is less lethal) compared to diazepam; one study stated that the LD_{50} values for etizolam were 2-5 times higher compared to diazepam.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

In 2014, etizolam was described by the Blue Ridge Poison Centre (in the United States of America) as an emerging drug of concern. The critical review reported a rise in the abuse of etizolam. In addition, an illicit market of etizolam was reported in Scotland but the exact scale was not stated. In Norway, etizolam was detected in 14 out of the 69 cases of driving under the influence of drugs (DUID) between July 2013 and May 2016. In 2 of these cases, etizolam was the only drug detected. Data was not available with regards to the illicit production of etizolam.

d. Need of the substance for medical (including veterinary) practice

Etizolam is authorized for use as a medicinal product in Japan, India and Italy. It is prescribed as an anxiolytic and used in the management of generalized anxiety disorder, panic disorder and mood disorders. It has been used to treat depressive symptoms and also psychiatric symptoms in children and adolescents. It is not listed in the 20th WHO Essential Medicines List or in the 6th WHO Essential Medicines List for Children. The report stated that it is produced for research in several countries. There is no evidence of veterinary use.

e. Need of the substance for other purposes (e.g. industrial)

Etizolam has no known industrial use.

f. Measures taken by countries to curb misuse

Etizolam is under national control in Denmark, Germany, Japan, and the United Kingdom. Etizolam is not currently listed under the Controlled Substances Act in the United States but it has been declared a controlled substance in Alabama, Arkansas, Florida, Mississippi, Virginia, Georgia, Indiana and recently in Arizona.

g. Impact if this substance is scheduled

Etizolam has similar pharmacologic features with classical benzodiazepines and most of the benzodiazepines are under international control. There should be no impact for legitimate use.

2. Are there absent data that would be determinative for scheduling?

Data on the misuse and abuse of etizolam are increasing but still minimal. There are no animal studies on the abuse potential of etizolam; in addition animal and human dependence potential data are relatively few.

3. Other comments or opinions

None

4. Expert reviewer's view on scheduling with rationale

The therapeutic usefulness of etizolam has been described. On the other hand, the evidence of etizolam misuse and abuse appear to have increased and etizolam abuse has been associated with fatalities (in most cases with multiple drug use). Its pharmacologic characteristics are similar to classical benzodiazepines which have been included in Schedule IV of the 1971 Convention: "*Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little to great."* However, in spite of an increased evidence of misuse and abuse of etizolam, it is difficult to describe its liability to abuse as constituting "a significant risk to public health" on the basis of these data. In view of this, I do not recommend scheduling at this time.