

ETIZOLAM
Critical Review Report
Agenda Item 4.13

Expert Committee on Drug Dependence
Thirty-ninth Meeting
Geneva, 6-10 November 2017

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Summary

Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in GABA_A receptors. It was developed in the 1980's as an alternative to known benzodiazepines. It is readily absorbed and it has a shorter half-life than benzodiazepines. It is sold commercially as a medicine to control generalized anxiety and other psychiatric pathologies in some countries. It is also sold in the internet by several companies for research purposes.

There have been a few studies comparing the differential pharmacological profile of etizolam compared to benzodiazepines. A major difference with benzodiazepines is its shorter half-life. It also differs from benzodiazepines as it has lower sedative effects. It has been proposed that this could be due to a lower affinity for GABA_A receptors containing alpha1-subunits.

In the last few years there has been an increase in its misuse and abuse, with several cases of death reported.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Etizolam

B. *Chemical Abstract Service (CAS) Registry Number*

0040054-69-1

C. *Other Chemical Names*

(4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine

2H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine, 4-(2-chlorophenyl)-2-ethyl-9-methyl-

AHR 3219

Y 7131

D. *Trade Names*

Arophalm (Nichi-Iko Pharmaceutical, Japan)

Capsafe (Ohara Yakuhin, Japan)

Depas (Abbott, Italy; Chong Kun Dang, South Korea; Tanabe Mitsubishi Pharma, Japan)

Depas 1% (Tanabe Mitsubishi Pharma, Japan)

Dezolam (Taisho Yakuhin, Japan)

E1 (Aarpik, India)

Eticalm (Towa Yakuhin, Japan)

Etisedan (Kyowa Yakuhin, Japan)

Etizola (Macleods, India)

Etizola Beta (*Etizolam and Propranolol*) (Macleods, India)

Etizolam Amel (Kyowa Yakuhin, Japan)

Etizolam EMEC (Sannova, Japan)

Etizolam KN (Kobayashi Kako, Japan)

Etizolam Nichi-iko (Nichi-Iko Pharmaceutical, Japan)

Etizolam Ohara (Ohara Yakuhin, Japan)

Etizolam SW (Medisa Shinyaku, Japan)

Etizolam TCK (Tatsumi Kagaku, Japan)

Etizolam Towa (Towa Yakuhin, Japan)

Etizolan (Kobayashi Kako, Japan)

Mozun (Tatsumi Kagaku, Japan)

New Zomnia (Molekule, India)

Nonnerv (Nisshin Pharmaceutical, Japan)

Palgin (Fujinaga Seiyaku, Japan)

Pasaden (Bayer, Italy)

Sedekopan (Choseido Pharmaceutical, Japan)

Sedekopan 1% (Choseido Pharmaceutical, Japan)

Sylkam (Dr. Reddy's, India)

E. Street Names

Etiz, Eitizzy, Etizest

F. Physical Appearance

White powder

G. WHO Review History

“The ECDD reviewed etizolam for the first time at its twenty-sixth meeting in 1989. At that time, the Committee rated the abuse liability of etizolam as moderate and the therapeutic usefulness as moderate to high. In view of the lack of clearcut abuse, and of public health and social problems associated with its use, the Committee was unable to come to a decision concerning the scheduling of etizolam and recommended that a decision be deferred until its twenty-seventh meeting. At its twenty-seventh meeting in 1990, the Committee again rated the abuse liability of etizolam as low to moderate and the therapeutic usefulness as moderate to high. The Committee noted few public health and social problems associated with its use at that time and considered that the degree of seriousness of these problems was not great enough to warrant international control. Consequently, the Committee did not recommend scheduling of etizolam in 1990.” (WHO Expert Committee on Drug Dependence, Thirty-seventh report). At the thirty-seventh ECDD, the committee pre-reviewed etizolam and recommended that a critical review of etizolam was warranted for a future meeting. The Committee noted deficiencies in information and suggested several potential sources that could be helpful in the preparation of the critical review, including those from traffic accident reports, seizure data, user forums, and pharmacovigilance data.

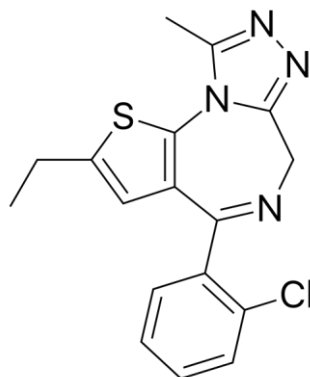
2. Chemistry**A. Chemical Name**

IUPAC Name: 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine

CA Index Name: N/A

B. Chemical Structure

Free base:



Molecular Formula: C₁₇H₁₅CIN₄S

Molecular Weight: 342.845 g/mol

C. Stereoisomers

None

D. Methods and Ease of Illicit Manufacturing

Etizolam is manufactured by several laboratories for clinical use in some countries and for research purposes. Thus, it is easily available by internet. There is no specific documentation of illicit manufacturing. However, it is now that the synthesis of thienotriazolodiazepine derivatives, such as etizolam, is complex or starts from a complex precursor such as thienodiazepine-2-one. Therefore, etizolam can only be manufactured in well-equipped laboratories. Synthesis routes of the thienotriazolodiazepines have been described in several patents (among others, US 8106189 B2; US 4201712 A; WO 2009/069147 A3; IN 2012DE02285 A 20140207).

The synthesis starting from the corresponding thienodiazepine-2-one has been described by Tahara et al. (1978). The method involves the replacement of the keto group in the thienodiazepine-2-one precursor by a hydrazino or acylhydrazino group, and the subsequent condensation of the hydrazino compound with an ortho-ester (or alternatively, with a carboxylic anhydride or a carboxylic acid halide) or the cyclisation of the acylhydrazino compound to yield the corresponding thienotriazolodiazepine. An improved method involves the cyclisation of R=N-NH-CO-CH₃ in toluene, where R has a thienodiazepine structure, with a catalytic amount of p-toluene sulphonic acid to obtain the corresponding thienotriazolodiazepine (Naik et al. 2012).

E. Chemical Properties

Melting point: 145-148°C

Boiling point: 545.3±60.0

Solubility: no soluble in water. Soluble in acid water and in polyethylene glycol and in ethanol.

F. Identification and Analysis

Chemical identification of etizolam in bulk and tablet formulations may be carried out by UV-spectrophotometric, colorimetric and liquid-chromatographic methods (Sakhreliya et al. 2012, Bhosale et al. 2013, Mondal et al. 2013, Mondal et al. 2015, Umamaheshwari et al, 2015). For the identification and quantification of etizolam in biological fluids, several gas-chromatographic and liquid-chromatographic methods with mass spectrometry or UV spectrophotometry as detection method are available (Fracasso et al. 1991, Inoue et al. 2000, Lee et al. 2003, Tanaka et al. 1996, Miyaguchi et al. 2006).

More recently, ultraperformance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) has been utilised for blood samples (Høiset et al. 2016). It has

also been shown that it is possible to detect etizolam with classical ELISA assay (O'Connor et al, 2016).

3. Ease of Convertibility Into Controlled Substances

Based on its chemical structure, it is not likely that etizolam can easily be converted into a controlled substance

4. General Pharmacology

A. *Routes of administration and dosage*

Etizolam is administered orally. The usual clinical dose is 0.5 to 2.0 mg/day.

B. *Pharmacokinetics*

Etizolam is readily metabolized in humans and animals by microsomal oxidation at its methyl and ethyl groups. The hydroxylated derivatives of etizolam are conjugated and excreted. (Fracasso et al, 1991). Etizolam has a half-life of about 6 hrs. Thus, as stated by Fracasso et al, 1991, it should be considered as a short acting benzodiazepine. It has been shown that etizolam metabolism is affected by CYP2C19 polymorphism (Fukasawa et al, 2005 and 2007).

C. *Pharmacodynamics*

Etizolam has similar pharmacological profile than benzodiazepines. It acts by allosterically potentiating chloride currents induced by GABA in GABA-A receptors. However, it has been shown some differences in its actions. Sanna et al. (2005) showed that etizolam induced lower tolerance than lorazepam in rats repeatedly treated with the drugs. It has also been shown that it possesses mainly anxiolytic effect but not sedative effects probably due to its lower intrinsic activity at $\alpha 1$ subunit-containing GABAA receptors (Sanna et al. 1999).

Etizolam is used, in some countries, for generalized anxiety disorder (Bertolino et al. 1989), panic disorder and to reduce anxiety. There is evidence that together with being useful to treat generalized anxiety disorder, it produce significant improve of depressive symptoms (Casacchia et al. 1990).

There is also a study showing that etizolam is useful to treat psychiatric symptoms in children and adolescents without or with minimal adverse effects (Nayak et al. 2016).

5. Toxicology

Frequent reported adverse effects are drowsiness and muscle weakness. There are only few studies of adverse effects of etizolam. In general, etizolam may cause similar adverse effects as the classical benzodiazepines, that is sedation, sleepiness, muscle relaxation, ataxia, slurred speech, and loss of consciousness, which are all responsive to the GABAA-receptor antagonist flumazenil (Baselt 2011, O'Connell et al. 2015). Occasionally, blepharospasms

(sustained involuntary closing of the eyelids) have been seen in patients (mostly woman) who had used etizolam for at least 1 month, most of them (28/35) for at least 1 year (Wakakura et al. 2004).

Several deaths have been described in which etizolam was analytically detected:

- Nakamae et al. (2008) described two cases. In the first case, the victim's heart blood contained 264 ng/ml etizolam, 7.2 ng/ml α -hydroxyetizolam, and 11 ng/ml 8-hydroxyetizolam (hydroxylation at the ethyl group); in the second case, the heart blood contained 26 ng/ml etizolam, 9.4 ng/ml α -hydroxyetizolam, and 9.3 ng/ml 8-hydroxyetizolam. In the first case, etizolam may have contributed to death; in the second case, the results do not suggest the contribution of etizolam to death.
- In a fatal case described by Karinen et al. (2014), etizolam (270 ng/ml) was found next to AH-7921 (330 ng/ml), methoxetamine (64 ng/ml), phenazepam (1330 ng/ml), 7-aminonitrazepam (43 ng/ml), diazepam (46 ng/ml), nordazepam (73 ng/ml), and oxazepam (18 ng/ml) in post mortem femoral blood. AH-7921 is a μ -opioid receptor agonist. In this case, is it likely that AH-7921 in combination with etizolam and phenazepam contributed to the death of the victim.
- Tanaka et al. (2011) described a fatal intoxication with multiple drugs, including etizolam (86 ng/ml), phenobarbital (5 mg/ml), promethazine (107 ng/ml), and chlorpromazine (144 ng/ml), measured in post-mortem femoral blood [abstract available in English]. According to the authors, use of multiple psychotropic medicines was the cause of death. The concentration of etizolam compared to that of phenobarbital does not suggest a contribution of etizolam to death.
- In an explicatory study of drug-related deaths recorded in the Scottish National Drug Related Death Database in 2012, one case was found in which etizolam, dihydrocodeine and tramadol were implicated in the cause of death. An evaluation of this latter case is not possible as concentrations in post-mortem blood were not presented. More recently, the National Records of Scotland listed 62 drug related deaths in 2014 in which NPS (new psychoactive substance) were implicated in, or had potentially contributed to the cause of death. In 40 of these cases, the only NPSs present were benzodiazepines (usually etizolam, but sometimes diclazepam or phenazepam). However, in all cases other substances were detected (e.g. opioids, alcohol) were detected.
- Etizolam (35 ng/mL) was detected along with MT-45 (520 ng/mL) in the femoral blood sample of a 35 year old man with a history of substance abuse. It was suggested that MT-45 was principally responsible for this death (Papsun et al. 2016).
- Etizolam detected in blood (0.3 mg/L) and urine along with other a number of other drugs in a fatal case study in Cyprus. The cause of death related to multidrug intoxication, attributed to the consumption of cathinones, designer benzodiazepines, and other drugs (Liveri et al. 2016).
- In Germany, etizolam was detected in femoral blood (280 μ g/L) and urine samples of one fatal case study along with other drugs including mitragynine and other

benzodiazepines. The cause of death was determined to be the aspiration of chyme by the subject, possibly due to a loss of consciousness (Domingo et al. 2017).

In mice, the median lethal dose (LD50) of etizolam was 4300 mg/kg when given orally, 800 mg/kg when given intraperitoneal, and > 5000 mg/kg when given subcutaneous (Tsumagari et al. 1978, Tahara et al. 1978). In rats, LD50 values were 3550 mg/kg, 850 mg/kg, and > 5000 mg/kg by oral, intraperitoneal and subcutaneous routes of administration, respectively. Compared to diazepam, the LD50 values for etizolam were 2-5 times higher (that is less lethality). In another study, LD50 values for etizolam and diazepam in mice were 560 mg/kg and 670 mg/kg, respectively, after intraperitoneal administration. When given orally, diazepam was more lethal than etizolam (LD50 690 mg/kg and 1780 mg/kg, respectively) (Johnson et al 1978).

6. Adverse Reactions in Humans

There is scarce information about the adverse reactions of etizolam. Wakakura et al (2004) reported the incidence of blepharospasm (sustained involuntary closing of the eyelids). O'Connell et al (2015) commented on the increase in patients highly sedated after ingestion of high doses of etizolam in emergency departments.

Other adverse effects associated with etizolam therapy included muscle weakness, slurred speech, ataxia, sleepiness, and sedation (Baselt 2011). Occasionally, blepharospasm has been seen in patients who use etizolam for more than 1 month. Paradoxical excitation is rare. A 17-months old girl accidentally took a tablet containing 0.5 mg of etizolam and developed paradoxical excitation with muscle weakness and motor incoordination which persisted for about 8 hours (Kato et al. 2007). Her plasma etizolam concentration shortly after admission to the hospital was 31 ng/ml.

7. Dependence Potential

The evidence showing lower tolerance for etizolam compared to benzodiazepines such as lorazepam (Sanna et al 2005) has been used to state that etizolam should have lower dependence liability. However, its dependence potential in humans has been documented (Gupta and Garg, 2014).

A. *Animal Studies*

Only few studies have addressed the potential dependence for etizolam. In a drug discrimination study in Rhesus monkeys, Woolverton et al. (1995) found that etizolam, like diazepam, fully substituted for pentobarbital.²³ The ED50 was 1.2 mg/kg for etizolam and 0.8 mg/kg for diazepam. Pretreatment with flumazenil shifted the dose-response curve to the right.

B. *Human Studies*

In general, the dependence and abuse potential of benzodiazepines are well known (Leonard BE 1999, Licata et al. 2008).

Few case reports deal with dependence of patients on etizolam. In 2014, Gupta and Garg documented the dependence potential of etizolam in the case of 23-year old man taking etizolam up to 2.5 mg per day. He was unable to stop etizolam use. The withdrawal symptoms were characteristic for benzodiazepine withdrawal (palpitations, impaired sleep, agitation, tremors). Nishii et al. (2014) described a 22-year old woman using 5 mg or more of etizolam per day. She was unable to stop medication by herself, but was successfully and fully tapered off using a dose reduction of 0.3 mg of etizolam per week. With this dose reduction regimen the patient did not experience withdrawal symptoms.

8. Abuse Potential

A. *Animal Studies*

No studies regarding the abuse potential for etizolam are found in PUBMED, and Google scholar.

B. *Human Studies*

There are increasing reports of abuse potential for etizolam (O'Connell et al. 2015).

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Etizolam is used clinically in some countries. Etizolam is an anxiolytic medicine, originally developed in Japan, where it was introduced under the brand name of Depas in 1984 (Yamawaki 1999). Etizolam is currently used as a prescription medicine in Japan, Italy, and India.

In a Japanese study on the prescription rate of benzodiazepines in outpatients with mood disorders in September 2002 (n=948 outpatients from 30 psychiatric hospitals/clinics in Tokyo), total benzodiazepines (including thienodiazepines) were prescribed to 63% of patients, whereas etizolam was prescribed to only 3.6%.⁶⁵ This study did not reveal a high prescription rate of etizolam in outpatients with mood disorders in Japan (Uchida and Suzuki 2009).

In its quality as PAF-receptor antagonist, etizolam has been clinically used to attenuate the recurrence of chronic subdural hematoma after neurosurgery (Hirashima et al. 2002, Hirashima et al. 2005)

10. Listing on the WHO Model List of Essential Medicines

Etizolam is not listed on the 20th WHO Essential Medicines List (EML) or on the 6th WHO Essential Medicines List for Children (EMLc)

11. Marketing Authorizations (as a Medicinal Product)

Yes, but only in some countries:

- Bayer, Italy
- Solvay Pharma, Italy
- Choseido Pharmaceutical, Japan
- Intas Pharmaceuticals Ltd, India
- Macleods Pharmaceuticals Ltd, India
- Sun Pharmaceutical Industries Ltd, India
- Tanabe Mitsubishi Pharma, Osaka, Japan
- Tatsumi Kagaku, Japan

12. Industrial Use

No known industrial use

13. Non-Medical Use, Abuse and Dependence

Concern has been raised on the non-medical use of etizolam and as stated by O'Connell et al (2015), there has been a rise in the abuse of etizolam.

In September 2014, The Blue Ridge Poison Centre (VA, USA) called etizolam an emerging drug of concern and said that there is an upward trend in US poison control center calls and in internet searches regarding this drug.

In a letter sent to the UK Home office from the Advisory Council on the Misuse of Drugs stating that etizolam is of concern. "has reportedly become the predominant benzodiazepine abused within the illicit drug market across Scotland and has been implicated in several deaths across the UK"

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

There are reports of the presence of etizolam in fatal cases (Nakamae et al. 2008), as described in Section 5. There is also report of increasing presence of affected individuals reaching emergency departments (O'Connell et al. 2015).

In Norway, etizolam was detected in 14 cases out of a total 77 samples (69 were driving under the influence of drugs (DUID) cases) collected between July 2013- May 2016, in 2 cases etizolam was the only drug detected. The median concentration of etizolam was 0.050 mg/L (0.019–0.17) in blood (Høiseth et al. 2016).

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

Etizolam is produced by several laboratories for clinical use in some countries and for research use in several countries. It is readily available by the Internet.

16. Illicit Manufacture and Traffic and Related Information

There are no reports of illicit manufacture of etizolam. Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

Etizolam is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Etizolam is under national control in Denmark, Germany, Japan, and the United Kingdom.

In United States, etizolam has not been authorized for medical use by the FDA. At present it is unscheduled but it is legal for research purposes. Some states have declared etizolam as a controlled substance. (Alabama, Arkansas, Florida, Mississippi, Virginia, and Georgia. In august 5, 2017, It will be controlled in Arizona. It is controlled in Indiana since July 1, 2017.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of Etizolam

Please refer to separate Annex 1 document published on ECDD website