Etizolam (INN)

Pre-Review Report

Agenda item 5.7

Expert Committee on Drug Dependence

Thirty-seventh Meeting

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World Health Organization

Contents

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Summary

Etizolam is a thienotriazolodiazepine and has pharmacological effects similar to those of the model benzodiazepine diazepam. It was developed in Japan and, at present, it is registered for use as a medicine in Japan, Italy, and India. Its main application is the treatment of generalized anxiety disorder with depressive symptoms. In this disorder, the therapeutic effect of etizolam (0.5 mg twice daily) is comparable to that of alprazolam (0.5 mg twice daily) and bromazepam (3 mg twice daily). At the recommended dose of 0.5 mg twice daily, etizolam appears to have minor effects on cognitive functioning.

Etizolam acts on the benzodiazepine site of the $GABA_A$ receptor. In isolated neurons, etizolam behaved as a full benzodiazepine receptor agonist, similar to nitrazepam and diazepam. In laboratory animals, etizolam induced muscle relaxation, reduces conflict behaviour, and had anticonvulsive activity. Depending on the parameter and the animal studied, etizolam is about as active or up to six times as active as diazepam. In a drug discrimination study, etizolam fully substituted for pentobarbital and pretreatment with flumazenil shifted the dose-response curve to the right.

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. These effects are responsive to the $GABA_A$-receptor antagonist flumazenil. Death by etizolam is rare. Only two cases have been described in the medical literature in which the concentration of etizolam in post-mortem blood indicate that etizolam may have contributed to death or was the likely cause of death. In animal studies, LD_{50} values for etizolam are 2-5 times higher (that is less lethality) than for diazepam.

Studies on abuse and dependence liability barely exist. In a study with Rhesus monkeys, etizolam fully substituted for pentobarbital in drug discrimination procedures. In man, two cases of dependence have been described in the medical literature. Some publications and reports suggest that etizolam is increasingly misused in the USA and in Europe.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Etizolam

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

40054-69-1

C. *Other Names*

6-(*o*-chlorophenyl)-8-ethyl-1-methyl-4H-*s*-triazolo[3,4-*c*]thieno[2,3-*e*][1,4]diazepine
4-(*o*-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine
4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine
1-methyl-6-*o*-chlorophenyl-8-ethyl-4H-*s*-triazolo[3,4-*c*]thieno[2,3-*e*]1,4-diazepine
Y-7131
AHR-3219

D. *Trade Names*

Depas, Etilaam, Etizest, Etizola, Etizolan, Pasaden, Sedekopan

E. *Street Names*

Etiz, Etizzy

F. *Physical properties*

Pure etizolam is a white odourless crystalline powder, practically insoluble in water and *n*-hexane, moderately soluble in aceton and ethanol, and soluble in methanol and chloroform.[1,2] Small colourless crystals may be obtained from ethyl acetate.[3] UV λ_{max} of etizolam in 0.1 M HCl: 252 nm and 293 nm.[4]

G. *WHO Review History*

The Expert Committee on Drug Dependence (ECDD) reviewed etizolam for the first time at its 26th meeting in 1989.[5] 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 clear-cut 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 to the 27th meeting of the Committee.

At its 27th meeting in 1990, the Committee again rated the abuse liability of etizolam as low to moderate and the therapeutic usefulness as moderate to high.[6] 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.

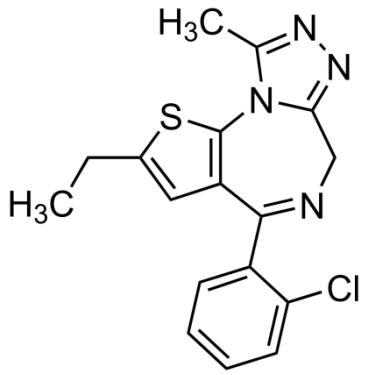
2. Chemistry

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: Not applicable

B. Chemical Structure

Free base:



Molecular Formula: $C_{17}H_{15}ClN_4S$
Molecular Weight: 342.8
Melting point: 147-148 °C[7]
Boiling point: unknown

C. Stereoisomers

No stereoisomers possible

D. Synthesis

Methods of manufacturing:
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).[7] 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-CH_3 in toluene, where R has a thienodiazepine structure, with a catalytic amount of p-toluene sulphonic acid to obtain the corresponding thienotriazolodiazepine.[8]

E. Chemical description

Etizolam is a heterocyclic compound with a diazepine ring fused to a thiophene ring and a triazolo ring. It belongs to the chemical class of the thienotriazolodiazepines. Etizolam has structural and pharmacological resemblance to the benzodiazepine class of medicinal drugs which have a diazepine ring fused to a phenyl ring.

F. Chemical properties

Etizolam is a weak base. It has a pK_a value of 2.76.[9]

G. Chemical identification

Chemical identification of etizolam in bulk and tablet formulations may be carried out by UV-spectrophotometric, colorimetric and liquid-chromatographic methods.[4,10-13] 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.[14-18]

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

Etizolam acts on the benzodiazepine site of the $GABA_A$ receptor. It has anxiolytic, sedative, muscle relaxant, anti-convulsant, and hypnotic properties.

A. Pharmacodynamics

Etizolam has pharmacological effects similar to those of the model benzodiazepine diazepam.[1,7,19] In laboratory animals (monkeys, dogs, cats, or mice), etizolam induced muscle relaxation and behavioural changes, and had anti-convulsive activity qualitatively similar to diazepam. Etizolam had a similar potency as diazepam on spinal reflexes and narcosis potentiation by hexobarbital and chloroprothixene. Loss of righting reflex in mice, however, occurred at higher doses compared to diazepam.

In a preliminary study, Tahara *et al*. (1978) found that etizolam decreased the number of fighting episodes and caused muscle relaxation in mice and cats, qualitatively comparable to diazepam but overall with a higher potency than diazepam (that is with lower ED_{50}

values).[7] Johnson and Funderburk (1978) found that etizolam inhibited tonic seizures in mice in doses comparable to those of diazepam, and produced muscle relaxation in mice in doses comparable to those of diazepam and in cats in doses less than those of diazepam.[19] Furthermore, the anxiolytic activity of etizolam as seen in tests of disinhibition and conflict behaviour was similar to that of diazepam.

In a study on the effect of etizolam in cats on the rage response induced by electrical stimulation of the medial hypothalamus, etizolam and diazepam produced a dose-dependent increase of the threshold for directed attack and, to a lesser extent, for hissing. In these tests, etizolam was about 6 times as potent as diazepam.[20]

In a study on the effects of several benzodiazepine and non-benzodiazepine compounds on GABA-induced responses in isolated frog sensory neurons, etizolam behaved as a full benzodiazepine receptor agonist and potentiated the GABA-induced chloride current 2.5 times the control level at a concentration of 3 µmol/L, similar to nitrazepam and diazepam.[21]

In sleep-disturbed rats, oral administration of etizolam for 7 days (1-5 mg/kg body weight) induced a concentration dependent shortening of sleep latency, an increase of non-REM sleep time, and a decrease of wake-time.[22] Abrupt withdrawal on day 8 caused a significant lengthening of sleep latency on withdrawal day (rebound effect), but there was no rebound effect of withdrawal on non-REM sleep time or wake time. The effects observed were similar to those of triazolam. Apparently in rats, the effects of etizolam and triazolam on sleep were comparable.

In a drug discrimination study in Rhesus monkeys, Woolverton *et al*. (1995) found that etizolam, like diazepam, fully substituted for pentobarbital.[23] The effective dose that gave a 50% response (ED_{50}) was 1.2 mg/kg for etizolam and 0.8 mg/kg for diazepam. Pretreatment with the benzodiazepine antagonist flumazenil led to a shift of the dose-response curve to the right.

A study into the effect of etizolam on the turnover and uptake of biogenic amines in rat and mouse brain revealed that etizolam has similar neurochemical effects as diazepam on serotonin and dopamine turnover and uptake, but differed from diazepam on noradrenaline turnover and uptake.[24] In contrast to diazepam, etizolam was able to decrease the turnover and to inhibit the uptake of noradrenaline in the mouse brain. These additional effects of etizolam on the noradrenergic system have been used to explain the anti-depressive activity that etizolam has in addition to its anxiolytic activity.

Sanna *et al*. (1999) studied the neurochemical and electrophysiological effects of etizolam on native rat brain $GABA_A$ receptors and in different human recombinant $GABA_A$ receptors expressed in *Xenopus laevis* oocytes.[25] Etizolam produced a concentration-dependent inhibition of [^{3}H]-flunitrazepam binding to rat cortical membranes with an IC_{50} (50% displacement of binding) of 4.5 nmol/L. Etizolam was more potent than alprazolam (IC_{50} 7.9 nmol/L) in this assay. In the oocyte model with different recombinant constructs, etizolam also potentiated the GABA-evoked chloride currents with less potency than alprazolam at the $\alpha_1\beta_2\gamma_{2S}$ construct and with similar potency as alprazolam at the $\alpha_2\beta_2\gamma_{2S}$ and $\alpha_3\beta_2\gamma_{2S}$ constructs. The benzodiazepine receptor antagonist flumazenil completely

blocked the effects of etizolam, as those of alprazolam, on the GABA-evoked chloride currents. Etizolam (0.5-3 mg/kg intraperitoneal) also produced a temporary and dose-dependent inhibition of basal acetylcholine release *in vivo* in hippocampus and prefrontal cortex of rat brain, with about three times higher potency than diazepam. From their results, Sanna *et al*. (1999) concluded that etizolam binds with high affinity to the benzodiazepine receptor site and that it may have a reduced intrinsic activity at specific subtypes of the $GABA_A$ receptor containing the α_1 subunit.[25]

In a subsequent study, Sanna *et al*. (2005) found that chronic exposure to etizolam has differential effects on the mRNA levels for the different $GABA_A$ receptor subunits in cultured rat hippocampal neurons.[26] Etizolam did not affect the mRNA levels for the α_1, α_2, α_3, and α_4 subunits but decreased the mRNA levels for the α_5 and the γ_{2S} subunit. In contrast, chronic exposure of lorazepam induced a decrease of α_1 and the γ_{2S} mRNA levels, an increase of α_3 mRNA levels, and no effect on the mRNA levels for the α_2, α_4, and α_5 subunits. The effects following subsequent withdrawal from etizolam on mRNA levels also differed from those of lorazepam. The main differences were in the levels of α_1 mRNA (no change after etizolam withdrawal; decrease after lorazepam withdrawal) and α_4 mRNA levels (no change after etizolam withdrawal; increase after lorazepam withdrawal). Both etizolam and lorazepam showed a persistent reduction of the γ_{2S} mRNA levels. Chronic exposure to and withdrawal of etizolam did not change the modulatory effects of etizolam and lorazepam on GABA-evoked chloride currents in cultured neurons, whereas chronic exposure to lorazepam reversibly reduced the modulatory effects of lorazepam on these currents. In addition and in contrast to lorazepam (1.0 mg/kg, intraperitoneal), chronic treatment of mice (three times per day for 21 days) with etizolam (1.5 mg/kg, intraperitoneal) did not result in a decrease of its anticonvulsive activity. Taken together, their results indicate that long-term treatment with etizolam (unlike lorazepam) does not induce substantial tolerance to its anticonvulsant activity and does not induce down-regulation of GABA mediated neurotransmission in rodents. According to the authors, the reduced intrinsic activity of etizolam at α_1-subunit-containing receptors might contribute to this persistent anticonvulsant activity of etizolam, as seen in mice.[26] This claim has been extended to suggest that etizolam might have a reduced liability for the development of tolerance and dependence in general. However, this claim has never been investigated and confirmed.

Human studies

Etizolam has been studied in the treatment of generalized anxiety disorder with depressive symptoms. Several studies in Italy showed the clinical effectiveness of etizolam (0.5 mg twice daily). The therapeutic effect was comparable to that of alprazolam (0.5 mg twice daily) and bromazepam (3 mg twice daily).[27-31] Etizolam appeared to be slightly more effective than the other two benzodiazepines in relieving somatic manifestations of anxiety.[28,30] Daytime drowsiness following treatment with either of the benzodiazepines was the main adverse effect reported by patients.

In a double-blind, placebo-controlled study on the effect of etizolam (0.5 mg twice daily) on cognitive functioning (Wechsler Adult Intelligence Scale and Digital Span Test), De Candi *et al*. (2010) found no significant differences in patients treated according to either a 3-week sequence of either etizolam-placebo-placebo or placebo-etizolam-etizolam.[32] In a

study on the acute and chronic effects of oral etizolam on P300 latency (indicator of cognitive functioning), Fukami *et al*. (2010) found that acute treatment (1 and 2 mg, orally) resulted in significant prolongation of P300 latency and that chronic treatment (1 mg, orally for 14 days) produced a weak non-significant prolongation of P300 latency.[33] These studies indicate that at the recommended dose of 0.5 mg twice daily, etizolam has only minor effects on cognitive functioning.

The effects of etizolam on human sleep have been studied by Nakazawa *et al*. (1975).[34] They found that etizolam (2 mg) increased total sleep time (on average from 489 to 547 minutes) and decreased the proportion of REM-sleep from 21% to 15% (unlike diazepam, 6 mg), which was not followed by a rebound elevation of REM-sleep in the following two nights. Etizolam (2 mg) had no effect on sleep latency (minutes), whereas diazepam (6 mg) reduced sleep latency. These results suggest that at the recommended dose of 0.5 mg BID, etizolam has small effects on sleep time and amount of REM-sleep.

Several studies showed that etizolam is a platelet-activating-factor (PAF) receptor antagonist. In clinical studies, etizolam is able to attenuate the recurrence of chronic subdural hematoma after neurosurgery.[35,36]

B. Routes of administration and dosage

Etizolam is supplied as the free base in 0.5-1 mg tablets for oral administration. The recommended dose is 0.5 mg two or three times per day.[32,37] Some authors reported higher dosages up to 4 mg of etizolam per day.[38,39]

C. Pharmacokinetics

Etizolam is well absorbed from the gastro-intestinal tract. The bioavailability in rats and mice was 95-100% after oral and intraperitoneal administration of a dose of 5 mg/kg of radiolabeled etizolam. The amounts excreted in urine and feces were 30% and 70% for rats, and 60% and 40% for mice, over a 3-day interval. In both animals, the elimination half-life was about 1.5 hours.[40] Several metabolites were detected, one of them being a hydroxylated metabolite.

In man, the kinetics of etizolam have been studied in healthy male volunteers (n=6) after a single oral dose (0.5 mg tablet) and after multiple oral dosing of 0.5 mg tablets at 12-hour intervals.[14] After a single dose, the peak plasma concentration (C_{max}) was 8.3 ± 1.7 ng/ml, time to C_{max} was 0.9 ± 0.7 hours, apparent distribution volume was 0.9 ± 0.2 L/kg, and plasma elimination half-life was 3.4 ± 0.3 hours (mean ± SD). After multiple dosing, C_{max} was 9.3 ± 1.7 ng/ml, time to C_{max} was 1.2 ± 0.7 hours, the average concentration was 3.4 ± 0.7 ng/ml, and the elimination half-life was 3.5 ± 0.3 hours. The estimated bioavailability was 87%. Interestingly, more recent studies reported much higher elimination half-lives of 12 ± 5.4, 11 ± 4.6, and 10 ± 3.9 hours for etizolam.[41-43] Baselt (2011) reported an elimination half-life of 7-15 hours, a distribution volume of 0.7-1.1 L/kg, and a biological availability of 93% for etizolam.[44]

Etizolam undergoes extensive biotransformation via hydroxylation and conjugation. The major metabolite in man is α-hydroxyetizolam (1'-hydroxylation, that is hydroxylation at

the methyl group). The pharmacological activity of this metabolite is comparable to that of etizolam. In the study by Fracasso *et al*. (1991), this metabolite reached a pre-next-dose steady state concentration of 4-5 ng/ml during multiple dosing.[14] Apparently, this metabolite accumulates in plasma at about twice the concentration of etizolam, due to its longer elimination half-life (mean 8.2 h).

In man, cytochrome P_{450} (CYP) isoform 3A4 is involved in the metabolism of etizolam as itraconazole, a specific inhibitor of CYP3A4, is able to increase total area under the plasma concentration-time curve (AUC) and elimination half-life of etizolam.[41] In addition, carbamazepine – an inducer of CYP3A4 activity – is able to decrease C_{max}, total plasma AUC and elimination half-life of etizolam.[43] In microsomes from insect cells expressing human CYP's, CYP3A4 appeared to be the main CYP enzyme involved in the metabolism of etizolam.[45]. CYP2C18 had about 25% of CYP3A4 activity, and CYP2C19 had about 5% of CYP3A4 activity towards etizolam. Nevertheless, the role of CYP2C19 may be clinically significant as poor metabolizers, characterized by CYP2C19 mutant alleles, had a higher total plasma AUC (287 ± 74 ng·h/ml vs 178 ± 122 ng·h/ml) and a longer elimination half-life (14.8 ± 4.2 h vs 10.5 ± 3.9 h) than extensive metabolizers after a single oral 1-mg dose of etizolam.[42]

5. Toxicology

Case reports describing the acute effects of overdosing of etizolam are scarce. 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 $GABA_A$-receptor antagonist flumazenil.[44,46] 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.[47] Blepharospasm is a female dominated disease that may be induced by benzodiazepine use. There is one case report of erythema annulare centrifugum in a 78-year old woman who had been using etizolam in a dose of 1 mg three times per day for three months (confirmed by patch testing with etizolam).[48]

Few deaths have been described with etizolam as a contributing factor or the cause of death. Nakamae *et al*. (2008) described two cases.[49] 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.[49] 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.[50] 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].[51] 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.[52] 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.[53]

In mice, the median lethal dose (LD_{50}) of etizolam was 4300 mg/kg when given orally, 800 mg/kg when given intraperitoneal, and > 5000 mg/kg when given subcutaneous.[1,7] In rats, LD_{50} values were 3550 mg/kg, 850 mg/kg, and > 5000 mg/kg by oral, intraperitoneal and subcutaneous routes of administration, respectively.[1] Compared to diazepam, the LD_{50} values for etizolam were 2-5 times higher (that is less lethality).[1]

In another study, LD_{50} 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 (LD_{50} 690 mg/kg and 1780 mg/kg, respectively).[19]

Three studies on fertility, development and teratogenicity in laboratory animals have been published in Japanese language [abstracts available in English].[54-56] When given orally to male rats for 63 days and to female rats for 14 days, etizolam (1, 5, and 25 mg/kg/day) had no significant effects on fertility, fetal mortality, and development.[54] When given to dams from day 17 of gestation to day 21 after delivery, etizolam (5, 25, and 100 mg/kg/day) inhibited body weight gain and spontaneous movements but had no significant effect on duration of pregnancy and delivery.[55] The development of offspring was normal when the dose was < 1 mg/kg.[55] When given to rabbits (5 and 25 mg/kg) and mice (100 mg/kg), etizolam inhibited growth; and when given to mice at 500 mg/kg/day, etizolam induced teratogenic effects.[56] The maximal safe dose of etizolam in pregnant mice, rats, and rabbits was 50, 25, and 0.25 mg/kg body weight/day, respectively.

No data are available on genotoxic and carcinogenic effects of etizolam.[57]

6. Adverse reactions in humans

The main adverse effect of etizolam reported in clinical studies on effectivity was drowsiness during daytime.[29] Other adverse effects associated with etizolam therapy included muscle weakness, slurred speech, ataxia, sleepiness, and sedation.[44] 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.[39] Her plasma etizolam concentration shortly after admission to the hospital was 31 ng/ml.

7. Dependence potential

A. Animal Studies

In a drug discrimination study in Rhesus monkeys, Woolverton *et al*. (1995) found that etizolam, like diazepam, fully substituted for pentobarbital.[23] The ED_{50} 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

The dependence and abuse potential of benzodiazepines are well known.[58,59] However, data on dependence and abuse of etizolam are barely available.

Few case reports deal with dependence of patients on etizolam. 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.[60] With this dose reduction regimen the patient did not experience withdrawal symptoms. Another case involved a 23-year old man taking etizolam up to 2.5 mg per day. He was unable to stop etizolam use.[61] The withdrawal symptoms were characteristic for benzodiazepine withdrawal (palpitations, impaired sleep, agitation, tremors). In these two publications, the authors refer to two Japanese publications (not available) that mention etizolam as the most abused drug of the benzodiazepine class of drugs in Japan. This information cannot be confirmed as these publications were not available.

8. Abuse potential

A. Animal Studies

No studies available

B. Human Studies

Etizolam has been widely prescribed as an anxiolytic and a hypnotic medicine to inpatients and outpatients in Japan. The prescription rate of etizolam is 9.9%.[62]

In a study examining overlapping prescriptions for psychotropic drugs in Japan, it was reported that in 119 patients the most frequent was etizolam (31.3%), followed by zolpidem (15.6%), brotizolam (14.3%) and triazolam (7.5%) (multiple responses).[63]

Japanese mental hospital survey on drug-related psychiatric disorders showed that the number of etizolam abusing patients was 120, followed by flunitrazepam (101), triazolam

(95) and zolpidem (53 patients) in 1,579 cases.[64] Therefore, the abuse potential of etizolam is relatively high.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Etizolam is an anxiolytic medicine, originally developed in Japan, where it was introduced under the brand name of Depas in 1984.[38] 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.

In its quality as PAF-receptor antagonist, etizolam has been clinically used to attenuate the recurrence of chronic subdural hematoma after neurosurgery.[35,36]

10. Listing on the WHO Model List of Essential Medicines

Not listed

11. Marketing authorizations (as a medicinal product)

Bayer, 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 data available

13. Non-medical use, abuse and dependence

In the last few years, concern has been raised on the non-medical use of etizolam. For example, the authors of several medical publications have mentioned that etizolam abuse has become a serious problem in Japan.[49] However, in the medical literature available in English, French, or German language only two cases of dependence have been described.[59,60]

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.[66]

As the synthesis of etizolam is complex, non-medical use of etizolam is likely to occur either by diversion from commercial sources or from patients who receive etizolam as

medication. In 2011, etizolam was notified for the first time as a NPS in the European Union.[67,68] Although etizolam is not a new substance, this notification probably reflects observed misuse of etizolam at that time.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

No data available

15. Licit production, consumption and international trade

Etizolam is produced by licensed pharmaceutical companies and distributed in conventional ways. Etizolam can easily be obtained via the Internet.

16. Illicit manufacture and traffic and related information

No data available

17. Current international controls and their impact

Etizolam is currently not under international control.

18. Current and past national controls

Etizolam is under national control in Germany since 2013. In the USA, etizolam is listed as a Schedule I drug in the state of Arkansas since 2014. Italy placed etizolam under national control in January 2015.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

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