



Critical Review Report:

ETIZOLAM

Expert Committee on Drug Dependence
Forty-second Meeting
Geneva, 21-25 October 2019

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Executive Summary

Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in GABA_A receptors. It is often referred to as a New (or Novel) Psychoactive Substance (NPS) benzodiazepine, or a 'designer' benzodiazepine. It differs from classic benzodiazepines through having a benzene ring replaced with a thiophene ring.

It is readily absorbed after oral ingestion and it has a shorter half-life than many benzodiazepines. It was patented in the 1970s and has been marketed since the early 1980s. It is sold commercially as a medicine in a limited number of countries (Japan, Italy and India). Etizolam is indication for treating generalized anxiety and other psychiatric pathologies. Trade names include Arophalm, Capsafe, Depas, Dezolam, Eticalm, Etidrale, Etisedan, Etizolan, Guperies, Medipeace, Mozun, Nonnerv, Palgin, Pasaden, Sedekopan and Sylazepam. Etizolam 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 preclinical study indicated that it may be less likely to induce tolerance compared to lorazepam, and may have lesser sedative effects compared to alprazolam and diazepam. It has been proposed that this could be due to a lower intrinsic activity at GABA_A receptors containing alpha1-subunits.

Etizolam was reviewed for the first time by the ECDD at its 26th meeting in 1989, and was reviewed most recently reviewed at the 39th meeting in 2017 where committee recommended to keep it under surveillance due to a the availability of minimal data on its abuse or dependence liability at that time. Since 2017, increasing reports have emerged describing large scale illicit production of pills containing etizolam in Scotland. Etizolam has been implicated in an increasing number of deaths, and is now the third most frequently detected drug in drug-related deaths in Scotland. Over the same time period, surveillance systems in Sweden and the US (where etizolam is not currently available as a registered medicine) have also documented increasing reports of exposures, with etizolam the most commonly reported 'designer' benzodiazepine in a study of US poisons calls.

A limited number of case reports describe dependence to etizolam in clinical settings, though reports of non-medical use are now common.

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
6H-tieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine, 4-(2-chlorophenyl)-2-etyl-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)
Dezolam (Taisho Yakuhin, Japan)
E1 (Aarpik, India)
Eticalm (Towa Yakuhin, Japan)
Etilaam (Intas Pharmaceuticals, India)
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)
Inxity (Archicare Limited, India)
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)

Zoly (Grownbury Pharmaceuticals, 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 clear evidence of nonmedical use, 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. At the thirty-seventh ECDD meeting, the committee pre-reviewed etizolam and recommended that a critical review of etizolam was warranted for a future meeting (World Health Organization & WHO Expert Committee on Drug Dependence, 2016). 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. At the thirty-ninth ECDD, the committee considered a critical review of etizolam.

At the 39th meeting it was considered that etizolam has some effects similar to those of diazepam (and other classical benzodiazepines), which is included in Schedule IV of the 1971 UN Convention on Psychotropic Substances (World Health Organization & WHO Expert Committee on Drug Dependence, 2018). It induces muscle relaxation, has anticonvulsive effects, potentiates sleep time, causes ataxia and substitutes for the pentobarbital discriminative stimulus, similar to diazepam. Nonmedical use and deaths were documented to be occurring in one country. Data on the abuse liability or dependence liability of etizolam were considered to still be minimal, making it difficult to describe its liability to use as constituting “a significant risk to public health”. The risks of etizolam nonmedical use were considered to appear to be relatively low.

The Committee recommended that etizolam be kept under surveillance. The Committee asked the Secretariat to request more data from Member States that may be affected by the misuse of etizolam, and which could facilitate a future review.

2. Chemistry

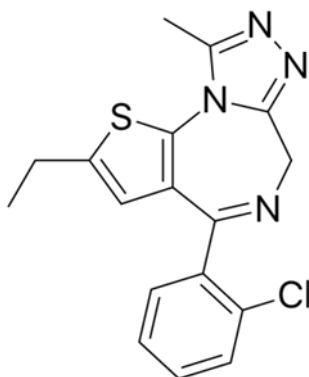
A. Chemical Name

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

Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in GABA_A receptors. It differs from classic benzodiazepines through having a benzene ring replaced with a thiophene ring.



Free base:

Molecular Formula: C₁₇H₁₅ClN₄S

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 are descriptions in online forums of the process for manufacturing processes that are readily available on the internet website Reddit (Reddit, 2018). Reports have emerged of large scale illicit manufacture and associated criminal proceedings (BBC News, 2018, BBC News, 2019). In these reports it is not stated if these operations were involved in illicit etizolam manufacture, or only the pressing of etizolam pills and subsequent distribution. It is known that the synthesis of thienotriazolodiazepine derivatives, such as etizolam, is complex or starts from a complex precursor such as thienodiazepine-2-one. Therefore, etizolam manufacture may require 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 AM, 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, Mondal et al., 2015, Mondal P, 2013, Umamaheshwari and Jayakar, 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, ultra performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) has been utilized for blood samples (Hoiseith et al., 2016). It has also been shown that it is possible to detect etizolam with classical immunoassay benzodiazepine ELISA assay in post mortem blood (O'Connor et al., 2016). Backberg et al. (2019) describe identification of etizolam in biological samples through initial screening of urine by multi-component liquid chromatography combined with high-resolution mass spectrometry (LC–HRMS) in full scan mode, following by subsequent re-analysis of screening-positive samples in parallel reaction monitoring (PRM) mode (LC–HRMS/MS).

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, with a maximum of 3mg/day. In one study in children (mean age 13.59 years, range 7-18 years, n = 57) mean doses of 0.67 ± 0.25 mg (0.25 to 1 mg)/day were reported (Nayak RB, 2016). Etizolam has been described to be approximately 6-10 times more potent than diazepam in its pharmacological effects based on pre-clinical studies, and 10 times more potent than diazepam for its hypnotic effects (Drug Enforcement Agency (DEA), 2018). Altamura et al. (2013) report that 1mg of etizolam is equivalent to 5mg of diazepam, a slightly lower potency than described by the DEA.

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 5-7 hrs (Altamura et al., 2013), and is considered a very short acting benzodiazepine. Cytochrome P450 CYP3A4 and CYP2C19 are involvement in the metabolism of etizolam (Araki et al., 2004, Fukasawa et al., 2007, Fukasawa et al., 2005). Carbamazepine, a CYP3A4 inducer, has been shown to increase the metabolism of etizolam (Kondo et al., 2005), and itraconazole, an inhibitor of CYP3A4, was shown to inhibit the metabolism of etizolam (Araki et al., 2004). CYP2C19 polymorphism has been shown to influence the extent of the drug-drug interaction between itraconazole and etizolam with poor metabolisers being at higher risk of a drug-drug interaction (Yamamoto et al., 2017). CYP2C19 deficiency may lead to side-effects or toxicity with etizolam (Fukasawa et al., 2007, Fukasawa et al., 2005).

Pharmacokinetic interactions have also been described with the traditional herbal formulas Kamisyoyosan and Tokisyakuyakusan, where CYP3A activity similar to grapefruit juice were seen in invitro experiments, though not in in vivo experiments (Makino et al., 2005). The authors concluded that at usual doses these herbal formulas would not cause clinically significant pharmacokinetic interactions with etizolam, however in the case of overdose this may become relevant.

In studies with healthy volunteers, etizolam concentrations reached a peaked of 0.008 mg/L following a 0.5 mg dose (Fracasso et al., 1991), and 0.018 mg/L after a dose of 1 mg (Kondo et al., 2005). The main metabolite of etizolam, α -hydroxyetizolam, formed via 1'-hydroxylation also has pharmacological activity comparable to that of etizolam, and has a longer half-life than etizolam (Fracasso et al., 1991). As such, α -hydroxyetizolam may contribute to the clinical effects of etizolam.

C. *Pharmacodynamics*

Etizolam has similar pharmacological profile to other benzodiazepines. It acts by allosterically potentiating chloride currents induced by GABA in GABA_A receptors. However,

some differences in its actions have been reported. Studies by Sanna et al. (2005) showed etizolam may be less likely to induce tolerance compared with lorazepam in rats repeatedly treated with the drugs. It has also been shown that it possesses mainly anxiolytic effects but not sedative effects probably due to its lower intrinsic activity at $\alpha 1$ subunit-containing GABA_A receptors when compared to diazepam and alprazolam (Sanna et al., 1999). Etizolam has been described to have some imipramine-like effects in preclinical studies (Drug Enforcement Agency (DEA), 2018).

A study of the effect of etizolam on cognition identified that in healthy subjects the auditory P300 event related potential was prolonged with etizolam, indicating a slower time to respond to an auditory stimulus, though tolerance to this affect appeared to develop with repeated administration of etizolam (Fukami et al., 2010). In the same study there was no effect of etizolam on neuropsychological tasks such as attention-needed tasks (trails making test, digit span) and memory (verbal paired associates, digit symbol).

A randomized double-blind study in 77 patients with anxiety found 0.5mg etizolam twice a day had no effect on cognitive function in patients with anxiety (De Candia et al., 2009). Consistent with this, an experimental study testing therapeutic doses (0.25mg and 1mg) of etizolam no effect on psychomotor performance was detected when assessed by the tracking, reaction time and vigilance tasks when compared to placebo (Busardo et al., 2019).

5. Toxicology

In mice, the median lethal dose (LD50) of etizolam was 4300 mg/kg when given orally, 800 mg/kg when given intraperitoneally, and > 5000 mg/kg when given subcutaneously (Tahara et al., 1978, Tsumagari 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 they were less lethal). 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 and Funderburk, 1978).

Frequent reported adverse effects include drowsiness and muscle weakness. In general, etizolam may cause similar adverse effects as the classical benzodiazepines, which are sedation, sleepiness, muscle relaxation, ataxia, slurred speech, and loss of consciousness, which are all responsive to the GABA_A-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). A case report of prolonged myocardial toxicity with tizanidine (48mg) and etizolam (24mg) coingestion was described by Amino et al. (2016). A report of seizure-like activity was reported with co-ingestion of novel stimulant, 3-fluorophenmetrazine, with a higher than usual dose of etizolam (Benesch and Iqbal, 2018).

Reports of 'designer benzodiazepine' exposures through the US National Poison System steadily increased from 2014-2017, with etizolam was the most common single agent exposure in each year of the study, responsible for 162 cases of the 324 single agent exposures reported (Carpenter et al., 2019). Reasons for exposure were documented as misuse (n = 24, 15%), abuse (n = 93, 57%), suspected suicide (n = 28, 17%) and Intentional–Unknown (n = 17, 11%). The number of cases increased each year with 26 in 2014, 30 in 2015, 46 in 2016 and 60 in 2017.

Initially case reports of deaths were 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.
- Karinen et al. (2014) described a fatal case where etizolam (270 ng/ml) was found in addition 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.
- Etizolam (35 ng/mL) was detected along with MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine) (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)
- One death associated with etizolam ingestion (unknown quantity) of etizolam was described in a report of poisons information calls from the US (Carpenter et al., 2019). No further information on whether etizolam was assessed to have a causal role in the death was documented.

The United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory on NPS Toxicology Portal (Tox-Portal), an online tool established in 2017 that collects data on toxicology and harm related to the use of NPS had 58 reports that involved etizolam. Most (41 reports) originated from the US, with the remainder from Korea (8), Thailand (1), Australia (1), Finland (5), Cyprus (1) and the UK (1). No reports were made from countries where etizolam is marketed. These cases were predominantly male (n =46, 79%), and represented mainly younger people (15-24, n = 24, 41%) and those aged 24-44 (n = 30, 52%), with four cases with a reported age of 45 years or older. One in four cases (n = 14, 24%) had more than one substances reported as involved in the case, often other novel psychoactive substance (for example U-4770). The cases included three reports of clinical admissions, 25 reports where samples were documented as ante-mortem samples, and 15 post-mortem samples. Twenty three cases were assessed to have a medium probability that etizolam contributed to the case, 12 cases assessed to have etizolam present but with a low probability of causality. The remaining cases were listed as undetermined or no assessments of contribution was reported.

In Scotland, the number of deaths attributed to etizolam has increased considerably in recent years. Etizolam was the third most frequently detected substance reported among all drug-related deaths in 2016, after heroin/morphine and methadone (Zawilska and Wojcieszak, 2019) and contributed to 46% of all drug-related deaths in Scotland in 2018 (National Records of Scotland, 2019). The number of deaths related to etizolam increased from 1 in 2012 to 223 in 2016, 299 in 2017 and 548 in 2018 (Table 1) (National Records of Scotland, 2019). Etizolam represents more than 80% of the 'street benzodiazepine' deaths in 2018 (548 of 675 deaths). In 2018, the majority of these deaths (74% or 405 of 548 deaths) were male, consistent with overall patterns in Scotland where 72% of decedents are male. Most deaths occurred in people aged 35-44 years old.

Table 1. Benzodiazepine-related deaths in Scotland 2009-2018 (National Records of Scotland, 2019)

Drug involved	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Diazepam	116	93	123	160	106	84	121	154	205	211
"All Prescribable benzodiazepines"	154	122	172	179	126	92	143	173	234	238
Etizolam	0	0	0	1	8	34	43	223	299	548
"All Street benzodiazepines"	1	0	14	20	40	41	58	303	432	675

6. Adverse Reactions in Humans

There is an emerging evidence base relating to adverse reactions related to etizolam use. Wakakura et al. (2004) reported the incidence of blepharospasm (sustained involuntary closing of the eyelids). O'Connell et al (2015) submitted a report on a patient who was highly sedated after ingestion of etizolam in the emergency department. In children gastro-intestinal adverse effects and sedation were reported (Nayak RB, 2016).

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. A case of withdrawal catatonia was reported following long-term use of etizolam 2-4mg daily (Banerjee, 2018). This case was not responsive to lorazepam and required electroconvulsive therapy. One published case from Japan [abstract published in English] describes a possible case of rare complication of benzodiazepine withdrawal syndrome, neuroleptic malignant syndrome on discontinuation of etizolam (Kawajiri et al., 2002).

7. Dependence Potential

There is evidence showing etizolam may have a lower ability to induce tolerance compared to benzodiazepines such as lorazepam (Sanna et al., 2005). This 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). Individual reports on harm-reduction and drug information forums such as Bluelight.org and Erowid.org describe large number of user reports describing tolerance, craving and withdrawal in addition to descriptions of pharmacology, drug effects and harm reduction advice pertaining to nonmedical use (Bluelight.org, 2019, Erowid.org, 2014).

A. *Animal Studies*

A limited number of studies have addressed the dependence potential for etizolam. In a drug discrimination study in Rhesus monkeys, Woolverton and Nader (1995) found that etizolam, like diazepam, fully substituted for pentobarbital, though etizolam appeared less potent. The ED50 was 1.2 mg/kg for etizolam and 0.8 mg/kg for diazepam. Pretreatment with the benzodiazepine antagonist flumazenil shifted the dose-response curve to the right, requiring higher doses to overcome the benzodiazepine antagonism.

B. *Human Studies*

In general, the dependence and abuse potential of benzodiazepines are well known (Licata and Rowlett, 2008, Lader 1994, Soyka, 2017). 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) (Gupta and Garg, 2014). 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 (Nishii et al., 2014).

8. Abuse Potential

A. *Animal Studies*

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

B. *Human Studies*

There are now numerous reports, including those on online forums, describing non-medical use of etizolam and harms relating to the non-medical use, though no human abuse liability studies were identified (O'Connell et al., 2015, National Records of Scotland, 2019, Gupta and Garg, 2014, Bluelight.org, 2019, Erowid.org, 2014).

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

Etizolam is used clinically in three 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 for generalized anxiety disorder. In a small double blind trial (n = 45) was shown to have equivalent anxiolytic effects when compared to alprazolam and bromazepam (Bertolino et al. 1989). In contrast to the other two drugs studied, the anxiolytic effects appeared to increase in the third and fourth week of treatment. In this trial by Bertolino et al. (1989), and also a second small double blind trial (n = 36) by Casacchia et al. (1990) there was also evidence improvement in depressive symptoms. Similarly, Savoldi et al. (1990) found that, in a trial of 30 patients with panic disorder with agoraphobia, that in the short-term (4 weeks) etizolam 0.5mg twice a day had meaningfully greater improvements in anxiety and depression compared to placebo. A trial by Pariente et al. (1989) compared etizolam and alprazolam in 30 female patients with generalized anxiety disorders associated with depressive symptoms. Difference between the drugs were not significant, though a trend towards earlier clinical response and greater effect on somatic symptoms with etizolam were described by the authors. The relative small sample sizes and short periods of follow up should be taken into account when considering this evidence.

An older review considering the role of benzodiazepines as adjunctive medications in schizophrenia highlighted the greater efficacy of higher-potency or higher dose benzodiazepine in management of acute agitation (Wolkowitz and Pickar, 1991). A later case report described a patient with auditory hallucinations that had not responded to other neuroleptics (Benazzi et al., 1993). In this case report repeated trials of etizolam were effective in suppressing auditory hallucinations, with their return on cessation of etizolam. A trial of etazolam did not show benefits in reducing this patients auditory hallucinations (Benazzi et al., 1993).

A randomized controlled trial in Japan (n = 144) examined the effect adding etizolam to the nonsteroidal anti-inflammatory drug mefenamic acid (Hirata et al., 2007). The study found no overall effect of etizolam on headache or shoulder pain, though among younger female patients a reduction in shoulder pain was noted.

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), benzodiazepines (including thienodiazepines such as etizolam) were prescribed to 63% of patients, though etizolam only made up a small proportion of this total, being prescribed to 3.6% of patients in this report (Uchida et al., 2009, Uchida and Suzuki, 2009). As such, this study did not reveal a high prescription rate of etizolam in outpatients with mood disorders in Japan (Uchida and Suzuki, 2009).

A small (n = 57) retrospective chart review provided preliminary evidence that etizolam can be used to treat psychiatric symptoms in children and adolescents, with 30 of the 37 children that were followed up showing at least minimal improvement, and three experiencing adverse effects (Nayak RB, 2016)

An in vitro study with rabbit platelets found that etizolam has activity as a platelet-activating factor (PAF) antagonist (Mikashima et al., 1987). PAF is an inflammatory mediator that appears to play a role in chronic subdural haematomas. Two small studies (one with 53 patients and the other with 48 patients) have demonstrated the potential role of etizolam in reducing volume of subdural hematomas (Hirashima et al., 2005, Hirashima et al., 2002) and etizolam has been clinically used to attenuate the recurrence of chronic subdural hematoma after neurosurgery.

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)

Etizolam has marketing authorization in the following 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

In 2014 descriptions of non-medical use of a range of forms of etizolam (including pharmaceutical pills, other manufactured pills and less commonly powders) were documented (Scottish Drug Forum (SDF), 2014). Cost to purchase pills ranged from £1 per pill for smaller quantities to 5p per pill for larger quantities, indicating meaningful bulk-purchase discounts in the illicit drug market. Concerns regarding non-medical use of etizolam were raised in 2015, with a case presenting to an emergency department with combined opioid and etizolam toxicity (O'Connell et al., 2015).

A 2016 letter sent to the UK Home office from the Advisory Council on the Misuse of Drugs referencing increasing harms with 'designer' benzodiazepines, stated that etizolam "has reportedly become the predominant benzodiazepine abused within the illicit drug market across Scotland and has been implicated in several deaths across the UK" (Advisory Council on the Misuse of Drugs (AMCD), 2016).

Non-medical use now appears to be widespread in Scotland as indicated by large volumes of etizolam that have been reported in drug seizures and the common identification of etizolam in drug-related deaths (BBC News, 2018, BBC News, 2019, National Records of Scotland, 2019).

Several studies now describe the rising prevalence of 'designer' benzodiazepine exposures over time, with etizolam the most common 'designer' benzodiazepine identified overall, or over a specific period of time (Backberg et al., 2019, Carpenter et al., 2019). A series of exposures were identified through the Swedish Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser (STRIDA) project. In English, this means "Collaboration project on toxicity and risk assessment of Internet drugs based on laboratory analyses". Results from monitoring emerging NPS benzodiazepines from the STRIDA project were published recently (Backberg et al., 2019). This study described increasing cases of NPS benzodiazepines from 2012, when the first case of any NPS benzodiazepine, etizolam, was detected to 2016 when funding changes resulted in a substantially reduced monitoring service (Backberg et al., 2019). The first reported case was a patient found unconscious after regularly consuming 3-4 etizolam pellets daily, with drug testing confirming the presence of etizolam. In the following years total NPS benzodiazepine detections increased from 37 cases in 2012 to 121 cases in 2015. In 2012 etizolam was the most commonly identified NPS benzodiazepine. Most etizolam cases (14 out of 20) were identified in the first year of monitoring, with other NPS benzodiazepine becoming more commonly detected after this time. All etizolam cases involved multiple substances. Ongoing illegal importation of etizolam was described in this report also.

A separate US study of poisons calls also found increasing exposures to 'designer' benzodiazepines reported, from 26 in 2014 to 112 in 2017, with etizolam accounting for 162 of 234 exposures (69%) (Carpenter et al., 2019). Finally, the DEA National Forensic Laboratory Information System (NFLIS) database also describes increasing reports relating to etizolam; from 3 in 2012 to 898 in 2017, with a total of 2,445 drug reports of etizolam from 44 states from 2012 through June of 2018 (Drug Enforcement Agency (DEA), 2018).

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

As described in Section 5 there are large increases in mortality attributed to Etizolam in Scotland, from the first report in 2012, to now being the third most common drug implicated in drug-related deaths in Scotland. There are reports of the presence of etizolam in fatal cases elsewhere also (Nakamae et al. 2008). There is an early case report of etizolam intoxication that was documented at a US emergency department (O'Connell et al. 2015).

In Norway, in a study of 22, 022 blood samples from criminal cases, etizolam was detected in 14 cases (Hoiseith et al., 2016). This represented 14 out of a total 77 samples that involved newer 'designer' benzodiazepines. Most cases (69 of the 77 cases) involving 'designer' benzodiazepines involved were driving who were under the influence of drugs. These cases were collected between July 2013 and 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.

A US study of poisons calls relating to 'designer' benzodiazepine exposures (primarily etizolam) reported common clinical effects of drowsiness/lethargy (59%) and slurred speech (17%), with 36% of cases requiring hospital admission (Carpenter et al., 2019). Exposures increased more than 500% between 2014 (n = 26) to 2017 (n = 160). Most of the 162 cases were described as 'misuse' or 'abuse' (72%), with smaller numbers documented as 'suspected suicide' (27%) or 'intentional-unknown' (11%). Severe effects and death were noted to be infrequent in this study.

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 now emerging reports of illicit manufacture and distribution of etizolam, with widely publicized reports of pill-pressing machines manufacturing etizolam pills "on an industrial scale" (1.6 million pills) identified in seizures in Scotland (BBC News, 2018, BBC News, 2019).

Project ION Incident Communication System (IONICS) is a secure online communication platform run by the International Narcotic Control Board (INCB) dedicated to real-time communication of incidents involving suspicious shipment of, trafficking in, or manufacture or production of NPS. Ten incidents involving etizolam have been communicated through IONICS to date. Two incidents took place in Estonia in 2015, one incident in United Kingdom

in 2016, two incidents in Netherlands and United Kingdom (1 each) in 2017, four incidents in Luxembourg (1), Netherlands (1) and Spain (2) in 2018, and once incident in Belgium in 2019. Netherlands and United Kingdom are identified as origins in two incidents respectively, Belgium in one incident and India in one incident. Origins are unknown in 4 incidents. While its prevalence is apparent only in countries in West and Central Europe only, it appears to persistently remain in the market.

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, Switzerland, Poland, the United Arab Emirates and the United Kingdom (Zawilska and Wojcieszak, 2019, Danish Health and Medicines Authority, 2013).

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 (Alabama, Arkansas, Arizona, Florida, Georgia, Indiana, Mississippi, Ohio and Virginia) have declared etizolam as a controlled substance. (Zawilska and Wojcieszak, 2019).

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

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances