Critical Review Report:
DICLAZEPAM

Expert Committee on Drug Dependence

Forty-third Meeting

Geneva, 12–20 October 2020

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Executive summary

Diclazepam is a 2-chloro derivative of the benzodiazepine diazepam. It consists of a benzene ring fused to a diazepine ring, with an R1 methyl group substitution and two substituted chlorine groups. Diclazepam was first synthesized in the 1960s but was never registered as a therapeutic product.

Diclazepam was first notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Early Warning System in 2013. It is commonly sold online as a research chemical, taken in doses of 1–4 mg (with 1–2 mg being a typical dose), and is also increasingly sold as falsified diazepam (or "street diazepam").

Diclazepam has a long elimination half-life of 42 hours, and is metabolized into the pharmaceutical benzodiazepines delorazepam, lorazepam and lormetazepam. It has similar pharmacological effects to the structurally similar diazepam, causing sedation and impairment of motor activity.

Reports from online forums describe diclazepam as having anxiolytic and hypnotic but not euphoric effects. It is commonly described as being used to self-medicate anxiety, as a sleep aid or to self-manage benzodiazepine and stimulant withdrawal. Diclazepam has long-acting effects, with reports of people having "blacked out" for many days after use. It is considered have lower recreational value than other benzodiazepines.

Diclazepam has been increasingly identified in blood samples from impaired drivers and has also been identified in samples related to drug-facilitated sexual assaults in China.

Diclazepam is monitored by the EMCDDA Early Warning System and 19 European Union countries have reported detections of diclazepam. The United Nations Office on Drugs and Crime (UNODC) Early Warning System reports data on diclazepam from 23 countries in four regions, resulting in a total of 62 reports from 2015 to 2019. Diclazepam is under national control in Finland, Denmark, Germany, the Republic of Korea, the Russian Federation, Switzerland, Turkey, the United Arab Emirates and the United Kingdom. Diclazepam has not previously been pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence, nor is it under international control.

1. Substance identification

A. International Nonproprietary Name (INN)

NA

B. Chemical Abstract Service (CAS) Registry Number

2894-68-0

C. Other chemical names

7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

chlorodiazepam

2'-chloro-diazepam

Ro 5-3448

2-chlorodiazepam

2'-chlorodiazepam

chlorodiazepam

2H-1,4-benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1-methyl- [ACD/Index Name]

7-chlor-5-(2-chlorphenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-on [German] [ACD/IUPAC Name]

7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1-methyl-2h-1,4-benzodiazepin-2-one

7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one [ACD/IUPAC Name]

UNII-070818R7PB

HSDB 6959

D. Trade names

No registered products

E. Street names

None found

F. Physical appearance

Diclazepam is a white powder. It is commonly sold as tablets, pellets and as a liquid, and online as a research chemical (Abouchedid et al., 2018).

G. WHO review history

Diclazepam has not previously been pre-reviewed or critically reviewed.

2. Chemistry

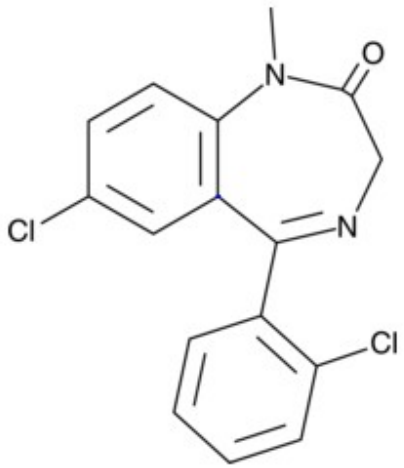
A. Chemical name

IUPAC name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

CA Index name: NA

B. Chemical structure

Diclazepam consists of a benzene ring fused to a diazepine ring, with an R1 methyl group substitution and two substituted chlorine groups.



Free base:

Molecular formula: $C_{16}H_{12}Cl_2N_2O$

Molecular weight: 319.2

C. Stereoisomers

None

D. *Methods and ease of illicit manufacturing*

Diclazepam is manufactured by several laboratories for research purposes and is easily available on the Internet (Abouchedid et al., 2018). Methods of synthesis have been described (Sternbach et al., 1962; Reeder and Sternbach, 1961), although information on the methods and ease of illicit manufacture was not found.

E. Chemical properties

Melting point: 217–219 °C

Boiling point: 524.6 ± 50.0 °C at 760 mmHg

Solubility: 20.5 mg/L at 25 °C

F. Identification and analysis

Diclazepam is detectable using a range of immunoassays commonly used in screening urine and blood samples for drugs (Pettersson Bergstrand et al., 2017; Behnke et al., 2019; O'Connor et al., 2016). For a 200 ng/mL concentration in serum and urine, a 72% cross-reactivity was reported for the cloned enzyme donor immunoassay (CEDIA) and 75% cross-reactivity was reported for the fluorescence polarization immunoassay (FPIA), indicating that not all cases of diclazepam use would be detected with this method (Moosmann et al., 2014). Furthermore, the risk of classification as either a false-positive for diazepam, or of attributing a positive immunoassay result to a pharmaceutical benzodiazepine, has been identified. This is because diclazepam breaks down into commonly used benzodiazepines, which can complicate the interpretation of assay results (Moosmann and Auwärter, 2018).

A range of approaches for the detection of diclazepam have been developed and validated. Blood and urine samples can be tested for diclazepam using liquid chromatography with tandem mass spectrometry (LC–MS-MS) (Mei et al., 2019; Pettersson Bergstrand et al., 2016) and urine can be tested with reversed-phase liquid chromatographic separation in combination with high-resolution mass spectrometry (LC–HRMS) (Pettersson Bergstrand et al., 2018). A microextraction technique based on ultrasound-assisted low-density solvent dispersive liquid–liquid microextraction (UA-LDS-DLLME) coupled with gas chromatography–triple quadrupole mass spectrometry GC-QqQ-MS has also been applied for the determination of diclazepam in urine samples (Meng et al., 2017).

Diclazepam has been analysed using an LC–MS-MS system including ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS-MS) (Helander et al., 2015; Høiseth et al., 2016; Lehmann et al., 2019; Tomková et al., 2017; Vårdal et al., 2018). A novel non-aqueous capillary electrophoresis – tandem mass spectrometry method for the simultaneous separation, identification and quantification of diclazepam down to concentrations of 1.5 ng/mL (as well as eight other designer benzodiazepines) in humans has also been developed and validated (Švidrnoch et al., 2018).

A study examining femoral blood and urine from an autopsy case was able to identify diclazepam and other novel benzodiazepines blood using QTRAP® (a technology that uses triple quad LC–MS-MS in addition to linear ion trap) (El Balkhi et al., 2017). Identification of diclazepam was achieved by detecting its Phase I metabolites lormetazepam and lorazepam.

Portable methods such as handheld Ramen spectroscopic techniques have also been shown to be able to identify diclazepam (Wallis et al., 2016).

A case report described use of full scan high-resolution mass spectrometry to reanalyse samples following updating of the library with additional novel psychoactive substances. This allowed identification of diclazepam with this retrospective screen, although it had not initially been identified as a contributing drug (Partridge et al., 2018). This report highlighted the usefulness of retrospective screening to identify novel benzodiazepines and other psychoactive substances. In this case, metabolites of diclazepam (lormetazepam (hydroxy-diclazepam), delorazepam (desmethyldiclazepam) and lorazepam (hydroxy-

desmethyl diclazepam)) were initially identified in both the blood and urine, but the presence of diclazepam was not confirmed until later.

3. Ease of convertibility into controlled substances

No information was found on the ease with which diclazepam can be converted into other controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Diclazepam is taken orally or sublingually. It is sold as a research chemical in 1, 5 and 10 mg pellets. Common doses reported in an analysis of reports from online forums were 2–4 mg (El Balkhi et al., 2020).

B. Pharmacokinetics

Data from a self-experiment with a single (1 mg) dose showed that diclazepam has an elimination half-life of 42 hours, and its three pharmacologically active metabolites (delorazepam, lorazepam, and lormetazepam) can be detected in urine for 6, 19, and 11 days respectively (Moosmann et al., 2014). Diclazepam is a 2-chloro derivative of diazepam that is metabolized into the prescription benzodiazepines delorazepam, lorazepam and lormetazepam (Moosmann et al., 2014).

Metabolic pathways and processes (dealkylation and hydroxylation) with biotransformation via a two-compartment model are similar to those of diazepam (Moosmann and Auwärter, 2018). Median blood concentrations of 0.025 mg/L diclazepam have been associated with impairment (Heide et al., 2020).

When administered acutely, diclazepam has been shown to be able to reduce oxycodone metabolism. When administered chronically, an increased production of oxymorphone (a more toxic metabolite of oxycodone), rather than the usual metabolic pathway to noroxycodone, was detected (Lawson et al., 2019). No effect of oxycodone on diclazepam metabolism was seen in this study. This study demonstrates the potential for diclazepam to contribute to increased oxycodone overdose if the two are used together.

Diclazepam has a plasma protein binding (PPB) value of 93.8%, suggesting it is less lipophilic than benzodiazepines such as phenazepam (PPB 98.3%) (Manchester et al., 2018b). Its experimental pKa1 is 2.31 ± 0.07.

C. Pharmacodynamics

Diclazepam has similar effects to diazepam, and people who use diclazepam report comparable tolerance and withdrawal symptoms (Cornett et al., 2018).

Estimates of diclazepam potency compared to diazepam vary by species. For example, diclazepam has been shown to have greater potency than diazepam in terms of impairment of motor activity and reducing conflict behaviour (e.g. choosing between food and avoiding a punishment) in studies with Sprague-Dawley rats (Babbini et al., 1979). Greater potency of diclazepam compared with diazepam in measures of sedation and

muscle relaxation was observed in cats, but not in mice (Sternbach et al., 1968). In studies with monkeys, diclazepam was not significantly different to diazepam at comparable doses of 1, 2 and 10 mg/kg, suggesting equivalent potency in this species (Bradley and Nicholson, 1984).

User reports suggest that effects last 5–12 hours (Manchester et al., 2018a).

5. Toxicology

No studies describing acute and chronic preclinical toxicology of diclazepam were identified.

6. Adverse reactions in humans

The long half-life of diclazepam (42 hours) may increase the risk of accumulation and intoxication (Moosmann et al., 2014). Published case reports describing acute nonfatal intoxication (*n* = 7) and death (*n* = 19) were identified, although diclazepam was not concluded to have contributed in every case.

Acute intoxication

France

- A case series of 18 cases of intoxication with diarylethylamines (ephenidine, diphenidine, and methoxphenidine) included 3 cases where diclazepam was also identified as an intoxicant (Eiden et al., 2018). These included:
- a 34-year-old male who experienced tachycardia, agitation, fever, sweating and obtundation;
    - a 20-year-old male admitted following a suicide attempt in whom methoxphenidine, diphenidine, 1P-LSD, pyrazolam, diclazepam, metizolam, flubromazepam, ethanol and heroin were documented; and
    - a 53-year-old male admitted with asthenia and somnolence in whom methoxphenidine, ephenidine, 5-EAPB, 3-MMC, BK-2C-P, AMT and diclazepam were identified.

Italy

- A 30-year-old man with a previous history of substance use was found in a confused, agitated and uncommunicative state with a Glasgow Coma Scale score of 9 (Gerace et al., 2017). A small plastic bag containing a few milligrams of a white powder labelled “Diphenidine 1 g” was found with him. Toxicological testing confirmed diphenidine in plasma and urine, and methylphenidate and diclazepam in the plasma, in addition to hospital-administered drugs and their metabolites in the urine and plasma. The authors concluded from the toxicology results that the drugs were likely to have been taken together within a short time. The plasma concentration of diclazepam found was 3.5 ng/mL.

Sweden

- A 39-year-old male who reported taking 3:4-dichloromethylphenidate and unknown tablets and powder spent 4 hours under medical observation with initial signs of agitation, pupil dilation and tachycardia. Diclazepam was identified in his urine (Bäckberg et al., 2019).
- A 45-year-old male was admitted to intensive care after reporting taking diclazepam, 2 mg and flubromazepam, 8 mg. He was febrile with agitation, dilated pupils and tachycardia. Flubromazepam was the only novel benzodiazepine detected in a urine sample taken 9 hours after admission. The authors noted that diclazepam may not be identified, as only the metabolites may be detectable (Bäckberg et al., 2019), with unmetabolized diclazepam not detected in all samples (Moosmann et al., 2014).

United States of America

- A 30-year-old male who was found unresponsive (Glasgow Coma Scale score of 3) was admitted to the emergency department (Runnstrom et al., 2020). He had non-reactive dilated pupils and required mechanical ventilation. Initial screening of urine for drugs was positive for lorazepam and cannabis. He improved over several days, although his condition was complicated by agitation and withdrawal symptoms that were managed with antipsychotics and benzodiazepines. He was extubated after 10 days. He reported use of 240 mg of diclazepam in liquid form purchased online for research use. The lack of routine testing for diclazepam was identified as a barrier to identification of its use in this case.

Deaths

Australia

- A 28-year-old male with a history of substance use (methamfetamine and a “benzo”) was found dead. His death was attributed to aspiration and mixed drug toxicity (Partridge et al., 2018). Initial screenings suggested that U-47700 was involved in the death. Retrospective screening identified additional compounds, namely diclazepam, flubromazepam and 2,5-dimethoxy-4-chloroamfetamine (DOC).

Cyprus

- A 42-year-old male with a history of serious mental illness was found unresponsive and could not be resuscitated (Liveri et al., 2016). White powder and a series of tablets were found at the scene. The powder was found to contain etizolam and diclazepam (based on matching mass spectral library information), while the tablets contained mirtazapine and olanzapine.

France

- A 41-year-old male with a well-established history of polydrug use and recent carfentanil intoxication was found dead. Autopsy specimens (blood and urine) revealed multiple substances including carfentanil, benzoylfentanyl, 4-fluobutyrylfentanyl, ethylhexedrone, diclazepam and methoxetamine, although death was thought to be attributable to carfentanil use (Dumestre-Toulet et al., 2019).
- A 31-year-old male was found dead with injecting equipment. Several small plastic bags labelled as deschloroetizolam, clonazolam, diclazepam and pyrazolam were identified on

the scene (El Balkhi et al., 2017). The autopsy revealed multiple organ congestion. Testing of femoral blood and urine revealed that diclazepam was present together with flubromazolam, deschloroetizolam, clonazolam, meclonazepam, flubomazepam, nixofepam and etizolam. Diclazepam was detected via the presence of its metabolites (lormetazepam and lorazepam), which were found at high concentrations in the urine. Diclazepam was absent in the blood and urine.

Germany

- A 21-year-old male with a previous history of substance use was found dead in the bath (Grumann et al., 2016). Urine and femoral blood samples obtained postmortem identified the metabolites of diclazepam in addition to methoxphenidine, 4-FA and evidence of alcohol consumption.
- A 27-year-old male was found dead with plastic bags at the scene labelled as containing diclazepam 2 mg, pyrazolam, 3F-phenmetrazine, 1-(2-fluorophenyl) propan-2-amine, and diphenhydraminhydrochloride, as well as one non-labelled plastic bag. The sample labelled as diclazepam was confirmed to contain diclazepam, and its metabolites were identified in blood, urine, pericardial and cerebrospinal fluid during autopsy, although at concentrations that were not likely to have been lethal. Death was attributed to positional asphyxia promoted by polysubstance intoxication.

Norway

- A study of samples from intoxicated drivers and other criminal offenders reported on 13 autopsy cases in which diclazepam had been identified. Median concentration of diclazepam in the blood was 0.0032 mg/L (range 0.0018–0.032 mg/L).

The UNODC Tox-portal identified four reports involving diclazepam. Two cases involved driving under the influence of drugs (in 2018–2019) in males from the age category 15–24 years old. Two further cases were reported from Finland and France, both postmortem samples, where little or no contribution of diclazepam was determined to be involved.

With the exception of one case where a high dose of diclazepam was consumed, most cases where diclazepam has been detected in connection with adverse events have involved the consumption of multiple substances and there is no clear evidence that diclazepam had a contributory role.

7. Dependence potential

A. *Animal studies*

No published studies were identified.

B. *Human studies*

No published studies were identified.

8. Abuse potential

A. *Animal studies*

No published studies were identified.

B. *Human studies*

No published studies were identified.

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

Diclazepam was developed by a pharmaceutical company but never tested in clinical trials (Wohlfarth et al., 2017).

10. Listing on the WHO Model List of Essential Medicines

Diclazepam is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

Diclazepam was synthesized and patented in 1961 (Reeder and Sternbach, 1961), but has never been marketed as a medicinal product.

12. Industrial use

Diclazepam has no known industrial use.

13. Nonmedical use, abuse and dependence

Diclazepam was first notified to the EMCDDA Early Warning System in August 2013 following a report from Germany (EMCDDA, 2013).

Two samples containing diclazepam were identified through the Swedish *Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser* (STRIDA) study in 2013 and 2014 (Bäckberg et al., 2018).

Content analysis of text from websites such as Drugsforum shows that diclazepam started appearing on the illicit marketplace between 2010 and 2015 (Del Vigna et al., 2016). Increasing reports of novel benzodiazepines (including diclazepam) have been documented in France (Batisse et al., 2020).

An analysis of a convenience sample (through the Global Drug Survey) of 2282 American respondents aged 16–60 years who had attended a nightclub in the past year found 12 respondents (0.53% of the sample) reported the use of diclazepam in their lifetime (Palamar et al., 2016).

The Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS) has published details of more than 70 samples where diclazepam was the main drug detected (Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS), 2020). These reports, published between 2014 and 2020, confirmed the presence of diclazepam in the samples. Initially the samples were predominantly tablets packaged and labelled as diclazepam, usually sold as reagents labelled "not for human use". Towards 2018 the frequency of samples increased. The more recent products were predominantly falsified diazepam, and occasionally contained more than one benzodiazepine (e.g. diclazepam with either alprazolam or etizolam).

The United States of America National Poisons Data System reported four cases of diclazepam poisoning in 2016 (*n* = 1) and 2017 (n = 3) (Carpenter et al., 2019). The United States of America National Forensic Laboratory Information System reported 203 instances where diazepam was identified in drug reports, increasing from 4 in 2014 to 63 in 2018 and 62 in 2019 (Communication to WHO, Cassandra Proileau). The UNODC Early Warning System reported data on diclazepam from 23 countries in four regions. A total of 62 reports were recorded from 2015 to 2019 (United Nations Office on Drugs and Crime (UNODC), 2020).

An analysis of 197 trip reports from online forums were published. The use of diclazepam was associated with anxiolytic and hypnotic effects and amnesia but not euphoria (El Balkhi et al., 2020). Those reporting diclazepam assigned it a high potency score, consistent with predicted binding affinity based on quantitative structure-activity relationship models (El Balkhi et al., 2020; Waters et al., 2018).

A study in Ireland examined samples from 200 participants receiving opioid agonist treatment (i.e. an opioid dependence treatment sample) (Mc Namara et al., 2019). The study identified two pharmaceutical benzodiazepines that are also metabolites of diclazepam (lorazepam and lormetazepam). The report did not reach a conclusion about prevalence of diclazepam use, most likely because of difficulties in differentiating between the use of lorazepam and lormetazepam and diclazepam in this study (Mc Namara et al., 2019).

Diclazepam has been described on consumer discussion forums as being commonly purchased as a sleep aid, to treat anxiety, for sedation and to self-treat benzodiazepine withdrawal or stimulant withdrawal (Abouchedid et al., 2018).

People on online forums describe diclazepam as leading to less euphoria compared with other faster onset benzodiazepines, like alprazolam, and describe it as having a lower potency compared with other benzodiazepines. They also describe occasions where people have blacked out for multiple days, attributed to its long half-life (Bluelight.org, 2020). Erowid.org had 17 reports on diclazepam; one described suicidal and psychotic symptoms after self-administration (Erowid.org, 2016), although most reports described diclazepam to be similar to other benzodiazepines like diazepam and lorazepam, albeit longer-acting.

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

User reports suggest that diclazepam is of low recreational value causing minimal cognitive impairment (Manchester et al., 2018a). The variable amounts of diclazepam contained in non-pharmaceutical products may contribute to public health problems, as larger doses than intended may be consumed due to variation in tablet contents (Moosmann et al., 2014). For example, 1 mg tablets were shown to contain between 0.59 and 1.39 mg diclazepam per tablet.

Instances of impaired driving following consumption of diclazepam appear to be increasing over time. An initial study examining samples associated with driving under the influence of drugs and other criminal offences (July 2013 – May 2016) identified 77 that involved novel benzodiazepines and diclazepam was identified in 15 of them (Høiseth et al., 2016). The mean blood concentration was 0.013 mg/L (range 0.0021–0.057 mg/L). In one case, involving an 18-year-old male, diclazepam was the only drug detected, with a blood concentration of 0.057 mg/L. The driver was assessed as "considerably impaired" (the highest rating possible).

A later study reported on the analysis of 575 samples (taken between June 2016 and September 2019), predominantly from intoxicated drivers and other criminal offenders in Norway. Of these samples, 334 contained diclazepam, making it the most frequently detected novel benzodiazepine (Heide et al., 2020). The median blood concentration was 0.0096 mg/L (range 0.0016–0.25 mg/L). In 16 cases, all involving driving under the influence of drugs, diclazepam was the only novel benzodiazepine identified. Tests on half (*n* = 8) of the samples also identified other substances including ethanol, nitrazepam and tetrahydrocannabinol or lorazepam, although the latter is likely to have been present as a metabolite of diclazepam. In most of these cases, impairment was assessed to be moderate to considerable, with diclazepam as the main contributor to impairment. Median blood concentrations in individuals judged to be impaired (0.025 mg/L) were higher than in cases where the individual was judged not to be impaired (0.0083 mg/L).

Diclazepam has been reported to have been involved in drug-facilitated sexual assaults in China (Pan et al., 2019). In a study of 31 cases of drug-facilitated sexual assault, for which 31 samples were available, diclazepam was identified in 6 of the 27 biological samples and 6 of the 9 liquor samples studied. A further report of a case of sexual assault involving diclazepam has been published in an abstract (Xiang et al., 2018).

The EMCDDA Early Warning System Network reported 34 deaths in which diclazepam was identified from biological samples (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020).

Four deaths involving diclazepam were reported in the United Kingdom between 2014 and 2016 (Pettie et al., 2018).

15. Licit production, consumption and international trade

Diclazepam is commonly sold online as a research chemical, labelled as not for human consumption (Cornett et al., 2018).

16. Illicit manufacture and traffic and related information

An analysis of Internet search engines detected a small increase in websites selling diclazepam between 2014 and 2016 (from 49 to 55) (Abouchedid et al., 2018). The price of diclazepam being sold as a research chemical had reduced over time, with considerable discounts for bulk purchasing. Bulk purchases were assumed to be for dealing or on-supplying to friends (Abouchedid et al., 2018).

A seizure of 99 850 tablets in Thailand were found to contain diclazepam (Official communication to the WHO ECDD Committee).

Diclazepam is monitored as a new psychoactive substance by the EMCDDA through the European Union (EU) Early Warning System. Nineteen EU countries have reported physical detections of diclazepam to the EMCDDA. Seventeen of these countries have reported approximately 2380 seizures, representing approximately 353 400 units of diclazepam, predominantly in tablet form (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020). In 2018, seizure data from the EU Early Warning System showed that novel benzodiazepines (etizolam, flubromazolam phenazepam and diclazepam) accounted for most (80%) of novel benzodiazepine seizures, although the proportions accounted for by each were not reported (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2018).

17. Current international controls and their impact

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

18. Current and past national controls

Diclazepam is not currently listed as a Schedule IV substance in the Controlled Substances Act in the United States of America (Cornett et al., 2018). Diclazepam would be captured under a group listing for benzodiazepines as a Schedule IV substance in Canada, although it is not individually listed (Government of Canada, 2020).

Diclazepam is under national control in Denmark, Finland, the Republic of Korea, Switzerland, Turkey and the United Arab Emirates (Zawilska and Wojcieszak, 2019). It is listed under the Misuse of Drugs Act 1971 in the United Kingdom as a Class C drug (UK Home Office, 2019), Germany (Federal Ministry of Justice and Consumer Protection Germany, 2020), and is a Schedule III controlled substance in the Russian Federation (Russian Government, 2020).

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 Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of DICLAZEPAM

Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on DICLAZEPAM

Region	Number of countries without information	Number of countries with information on substance
African Region	15	1
Eastern Mediterranean Region	7	4
European Region	21	17
Region of the Americas	9	4
South-East Asia Region	4	2
Western Pacific Region	4	4
Total 92	**60**	**32**

LEGITIMATE USE

One country (Region of the Americas) reported approved human medical products and veterinary products containing DICLAZEPAM.

Two countries (one European Region, one Region of the Americas) reported DICLAZEPAM being currently used in medical or scientific research (excluding use as an analytical reference standard), specifically “in cell line studies (binding/functional assays) and animal studies”.

Two countries (one Region of the Americas, one Western Pacific Region) reported DICLAZEPAM being used in industrial or other non-medical or non-scientific use.

One country (Region of the Americas) reported therapeutic indications approved for DICLAZEPAM: “Benzodiazepines are commonly used for sedative, anxiolytic and amnestic effects in medical diagnostic and therapeutic procedures”.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Twelve countries reported that DICLAZEPAM is being misused or abused for its psychoactive properties/recreational use.
The most common known route of administration reported was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	11
Injection	1
Inhalation	0
Sniffing	1
Smoking	0
Don't know	18

The most common known formulation of DICLAZEPAM reported was tablets (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	8
Tablets	10
Liquid for oral use	1
Solution for injection	0
Don't know	16

To the above, countries added:

- trips, capsules
- green capsules.

Eleven countries reported the level of negative health impact due to DICLAZEPAM's non-medical consumption as "serious" or "substantial" (Table 4).

Table 4. Numbers of countries reporting levels of negative health impact of DICLAZEPAM

Serious	Substantial	Negligible	Don't know
5	6	7	13

Four countries (four European Region) reported emergency room admissions related to the non-medical use of DICLAZEPAM.

As for reported adverse effects, one country (European Region) noted "lowering consciousness". One country (European Region) noted, "Difficulty listing the side-effects attributed to DICLAZEPAM because context of polyconsumption the most often".

No countries reported users of DICLAZEPAM presenting for drug dependence treatment.

Regarding mortality, only two countries (two European Region) reported deaths involving DICLAZEPAM:

- two fatal cases where other substances were also involved (2016)
- one fatal case where other substances were also involved (2019).

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Fifteen countries responded that DICLAZEPAM is currently controlled under national legislation to regulate its availability.

Table 5 shows the main reported activities involving DICLAZEPAM.

Table 5. Reported illicit activities involving DICLAZEPAM

Activities	Number of countries
Smuggling from other countries	5
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	1
Trafficking	4
Diversion from legal supply chain	0
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	2
Don't know	18

To the above, countries added:

- trafficking through postal services
- Internet sales (with no other information).

Eleven countries reported seizures (Table 6).

Table 6. Reported seizures of DICLAZEPAM

Year	Seizures
2020	13
2019	138
2018	131
Total	**282**

Twenty-seven countries have the forensic laboratory capacity to analyse DICLAZEPAM.

One country (European Region) commented, "Forensic laboratories have the capacity to analyse DICLAZEPAM if reference material is available".