



Critical Review Report: CLONAZOLAM

Expert Committee on Drug Dependence
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Executive summary

Clonazolam is the most potent of a series of 1-4 triazolobenzodiazepines. It was first synthesized in 1971, but was not licensed for therapeutic use. Clonazolam is a triazolo-analogue of the registered drug clonazepam. Clonazolam is sold in powdered form as well as in blotter, liquid and tablet form. In recent years clonazolam has been increasingly sold as falsified benzodiazepines (commonly as diazepam and alprazolam).

Clonazolam cross-reacts with common benzodiazepine immunoassays, and can be detected in blood with liquid chromatography with tandem mass spectrometry, and in urine and serum using liquid chromatography–high-resolution mass spectrometry. Clonazolam is typically found in low concentrations as the parent compound in urine. The use of low cut-offs and screening for the parent metabolite is recommended.

Doses are generally low due to its high potency (e.g. 0.2–0.4 mg). Adverse reactions involve severe sedation which sometimes requires flumazenil treatment. Toxicology studies on large samples of impaired drivers have identified clonazolam, albeit less frequently than other novel benzodiazepines. In recent years, large increases in seizures of clonazolam have been reported in the United States of America (USA).

Clonazolam is under national controls in the United Kingdom and Sweden, and has been classified as a schedule I drug in the USA state of Virginia. Clonazolam 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*

33887-02-4

C. *Other chemical names*

UNII-HJH52YYC1X

HJH52YYC1

33887-02-4

SCHEMBL11681332

XJRGLCAWBRZUFC-UHFFFAOYSA-N

DTXSID301014166

ZINC39206261

DB14716

Q19607410

4H-(1,2,4)triazolo(4,3-a)(1,4)benzodiazepine, 6-(2-chlorophenyl)-1-methyl-8-nitro-6-(2-chlorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine
6-(2-chlorophenyl)-1-methyl-8-nitro-4H-s-triazolo[4,3-a][1,4]benzodiazepine
8-nitro-1-methyl-6-(o-chlorophenyl)-4H-s-triazolo-[4,3-a][1,4]benzodiazepine
8-nitro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo[4,3-a][1,4]-benzodiazepine
6-(2-Chlorophenyl)-1-methyl-8-nitro-4H(1,2,4)triazolo(4,3-a)(1,2,4)triazolo(4,3-a)(1,4)benzodiazepine

D. *Trade names*

Reported to be sold also as clonitrazolam (Ghazi and Mohamand, 2017).

E. *Street names*

Clon

Clam, C-lam (Trott, 2019)

F. *Physical appearance*

Clonazolam is sold in powdered, blotter, liquid and tablet form (Cornett et al., 2018; Dowling et al., 2018; Murphy et al., 2019).. Clonazolam is often sold as falsified pharmaceutical benzodiazepine products in tablet form, and it is also taken in liquid form (Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS), 2020; El Balkhi et al., 2020).

H. WHO review history

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

2. Chemistry

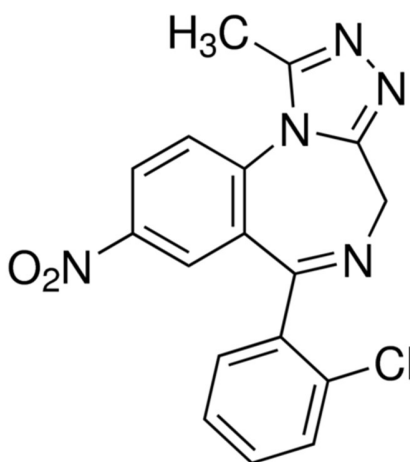
A. Chemical name

IUPAC name: 6-(2-Chlorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

CA Index Name: NA

B. Chemical structure

Clonazolam is a triazolobenzodiazepine, with a 1-methylated triazole ring fused to the diazepine ring. It is a potent derivative of clonazepam and alprazolam (Cornett et al., 2018).



Free base:

Molecular formula: C₁₇H₁₂ClN₅O₂

Molecular weight: 353.9 g/mol

C. Stereoisomers

None

D. Methods and ease of illicit manufacturing

Methods of small scale-synthesis for forensic use have been published (Dowling et al., 2018). No literature was found describing illicit manufacture, although purchase as a research chemical is commonly described.

Methods of synthesis of triazolo analogues from available 1-4 benzodiazepines have been described (Hester and Von Voigtlander, 1979; Moosmann and Auwärter, 2018).

E. Chemical properties

Melting point

Not reported

Boiling point

576.0 ± 60.0 °C at 760 mmHg

Solubility

0.0426 mg/mL in water

F. Identification and analysis

Clonazolam has sufficient cross-reactivity to trigger a positive result on urine screening using common commercial benzodiazepine immunoassays. However, these immunoassays cannot distinguish between prescribed benzodiazepines and clonazolam (Pettersson Bergstrand et al., 2017).

Clonazolam has been detected in blood samples using liquid chromatography with tandem mass spectrometry (LC-MS-MS) (Høiseth et al., 2016; Mei et al., 2019) and in urine and serum using liquid chromatography–high-resolution mass spectrometry (LC-HRMS) (Pettersson Bergstrand et al., 2018; van Wijk et al., 2019; Židková et al., 2019). The metabolite 7-aminoclonazolam has been identified in urine using nano-liquid chromatography-high-resolution mass spectrometry (nanoLC-HRMS/MS) (Meyer et al., 2016). Clonazolam is typically found in low concentrations as the parent compound in urine (e.g. 7–23 ng/mL) (Pettersson Bergstrand et al., 2016). For this reason, screening for the metabolite is recommended (Meyer et al., 2016; Mc Namara et al., 2019). A lower cut-off of 10 ng/mL has been recommended for clonazolam (Pettersson Bergstrand et al., 2018).

A case report described testing of a drug sample (unconsumed tablets). Clonazolam was identified in the tablets using ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UHPLC-QToF) (Pope et al., 2018). Neither clonazolam or its metabolites were identifiable in the patient's urine. However, it is unclear if this was due to limitations of the testing procedure, or because the contents of the unconsumed tablet were different to the consumed tablet.

A study examining femoral blood and urine from an autopsy was able to identify clonazolam and other novel benzodiazepines in the urine but not in the femoral blood using QTRAP® (a technology that uses triple quad LC-MS-MS in addition to linear ion trap) (El Balkhi et al., 2017).

3. Ease of convertibility into controlled substances

No information was found on the ease with which clonazepam is converted into a controlled substance.

4. General pharmacology

A. *Routes of administration and dosage*

Oral administration with common doses of 0.2–1.0 mg has been reported (Moosmann and Auwärter, 2018; El Balkhi et al., 2020).

B. *Pharmacokinetics*

The elimination half-life of clonazepam is estimated to be 3.6 hours (van Wijk et al., 2019). Clonazepam is extensively metabolized and is mainly excreted as its amino and acetamino metabolites (Meyer et al., 2016). It has a medium-length onset of action (20–60 minutes) (Cornett et al., 2018). The main metabolites are 7-aminoclonazepam, hydroxyc lonazepam, and 7-acetamidoclonazepam (Murphy et al., 2019). Both metabolites and parent compound are eliminated in the urine. No information is available on volume of distribution (Murphy et al., 2019). Serum concentrations of 6.8 ng/mL were identified in a person intoxicated with multiple substances (Židková et al., 2019)

C. *Pharmacodynamics*

Clonazepam is a triazolo-analogue of the registered drug clonazepam (Huppertz et al., 2015). As with all benzodiazepines, clonazepam achieves its pharmacological effect by allosterically potentiating chloride currents induced by gamma-aminobutyric acid (GABA) in GABA_A receptors. Clonazepam produces sedation, muscle relaxation, loss of motor control, amnesia and respiratory depression, and does not appear to induce cross-tolerance with other benzodiazepines (Cornett et al., 2018).

5. Toxicology

Initially synthesized in 1971 together with a series of 1-4 triazolobenzodiazepines with high central nervous system depressant activity, clonazepam was found to be the most active substance in the series. It was effective at test doses of less than 10 µg/kg in mice, with death occurring at a median effective dose (ED₅₀) of 0.005 mg/kg, and the ED₅₀ for antagonism of foot shock was 0.031 mg/kg (Hester et al., 1971). In these preclinical studies, high potency was demonstrated in tests measuring loss of righting reflex, antagonizing pharmacological effects of drugs like nicotine and strychnine as well as electric shock and foot shock, in addition to potentiating effects of alcohol and pentobarbital (Hester et al., 1971).

A quantitative structure–activity relationship (QSAR) approach showed that clonazepam has a very high binding affinity compared with “classic” benzodiazepines (Waters et al., 2018). Clonazepam was the second most potent benzodiazepine examined in that study.

6. Adverse reactions in humans

Common clinical effects of clonazolam poisoning identified through the USA National Poisons Data System include drowsiness/lethargy (68% of cases), slurred speech (16%) and tachycardia (14%) (Carpenter et al., 2019). In most cases (80%) effects were assessed to be mild-to-moderate, usually lasting up to 24 hours (Carpenter et al., 2019). These cases were most commonly managed with fluids (34%), although three cases were managed with the benzodiazepine antagonist flumazenil.

Nine case reports (eight emergency department or intensive care admissions and one autopsy) involving clonazolam were identified.

Australia

- A case report described a 32-year-old male in treatment for opioid dependence (taking methadone, 50 mg daily) who had fallen from his chair onto the ground after taking “pink and purple tablets like lollies” (Pope et al., 2018). He required supplemental oxygen to maintain an oxygen saturation of > 94%, and had a Glasgow Coma Scale (GCS) score of 10. An initial screening of urine for drugs was positive for benzodiazepines. Further investigation identified doxylamine, clonidine, oxazepam, temazepam, methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, which were felt did not explain the presentation. Additional analysis of the tablets using UHPLC-QToF determined that each tablet contained 16 mg of clonazolam and 0.18 mg of flubromazolam. Flubromazolam was subsequently detected in the patient’s urine, although clonazolam was not, possibly because it was below the detection level, had been excreted or was not consumed. The patient was discharged after 15 days following a lengthy stay in intensive care.

Czech Republic

- A 26-year-old male was found unconscious (GCS, 3) and required admission to intensive care with artificial ventilation (Židková et al., 2019). Extubation occurred after 12 hours, and discharge after 40 hours. The substances identified in the serum and urine were clonazolam, U-47700, tetrahydrocannabinol, citalopram and midazolam.

France

- Injecting material and several small plastic bags labelled as deschloroetizolam, clonazolam, diclazepam and pyrazolam were identified at the scene where a dead 31-year-old male was found (El Balkhi et al., 2017). The autopsy found multiple organ congestion. Testing of femoral blood and urine revealed presence of clonazolam as well as flubromazolam, deschloroetizolam and meclonazepam, diclazepam, flubomazepam, nixofepam and etizolam.

Poland

- A 26-year-old female was admitted to hospital following intentional consumption of clonazolam powder (10 mg) to treat poor sleep due to a persistent cough (Sommerfeld-Klatta et al., 2020). The patient was unconscious (GCS score, 3) on

admission and tachycardic, possibly due to underlying infection and fever associated with bronchitis. A high concentration of clonazepam in the blood (0.077 mg/L) was measured. After 24 hours the patient was still falling asleep when left unstimulated, but no flumazenil was required. She was discharged after eight days. No mental health or substance use disorder was identified.

United States of America

- Two presentations at an emergency department in Ohio were described. Laboratory analysis of the samples of the tablets involved confirmed that they were clonazepam (Jolliff et al., 2016):
 - A 20-year-old male, who was found slumped in his car after taking 2.1 mg of clonazepam (3 × 0.7 mg tablets). He became hypotensive and bradycardic and responded to intravenous fluids. His urine showed benzodiazepines only.
 - An 18-year-old male in the same car fell asleep after taking 1.4 mg clonazepam. He had tachycardia and hypertension (in contrast to the first case). His urine tested positive for opioids, cannabis and benzodiazepines.
- A 28-year-old male presented to a USA emergency department with somnolence after ingesting approximately 15 mL of a product labelled as a clonazepam 0.5 mg/mL in ethyl alcohol and propylene glycol (Murphy et al., 2019). He was observed in the emergency department, where his vital signs were normal, returning to baseline mental status after 6 hours.
- A 25-year-old male with a long history of polysubstance use was treated for confusion, visual hallucinations, acute agitation and aggressive behaviours during a hospital stay (Ghazi and Mohamand, 2017). He reported a recent history of use of benzodrine inhalers and had taken 100 mg of clonazepam over a two-day period prior to hospital admission.
- A 34-year-old male attended the emergency department in a state of somnolence and confusion that lasted for more than 6 hours (van Wijk et al., 2019). Samples of tablets he had taken contained clonazepam (the tablet contained 1.1 mg, although marked 0.5 mg) and etizolam (2.4 mg, although marked 1.2 mg).

An unpublished communication to WHO referred to at least 21 ante- and postmortem overdose events that have involved clonazepam in the USA since 2012 (Unpublished communication, 2020). Seizure events involving clonazepam were noted to have been rising at a faster rate than those associated with other substances. The same communication indicated that the Center for Forensic Science Research and Education in the USA has identified at least nine forensic events, like postmortem toxicology and human performance testing, that have involved clonazepam since 2018.

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

Clonazepam has never been licensed for therapeutic use.

10. Listing on the WHO Model List of Essential Medicines

Clonazepam is not included in the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

None

12. Industrial use

Clonazepam is sold as a research chemical and reagent (Huppertz et al., 2015; Lembke et al., 2018).

13. Nonmedical use, abuse and dependence

Clonazepam was first detected on the drug market in 2014 (Moosmann and Auwärter, 2018), and the first reported seizure occurred in Sweden in October 2014 (Bäckberg et al., 2019). The Swedish *Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser* (STRIDA) study identified 16 confirmed cases involving clonazepam intoxication in Sweden, most in 2015. The USA National Poisons Data System reported 50 cases of clonazepam poisoning during 2016 ($n = 14$) and 2017 ($n = 36$), making it the second most common single-agent exposure after etizolam (Carpenter et al., 2019). Poisonings typically occurred in younger males (84% males, median age 26 years, range 15–50 years), with most cases representing acute exposure in the context of “abuse” (60%) and suspected suicide (20%) (Carpenter et al., 2019).

The Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS) published details of 24 samples where clonazepam was the main drug detected (Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS), 2020). Of these, 13 samples were purchased as either diazepam or alprazolam. Most of the samples tested appeared as blue, green, red or white “brick”-like tablets (sold as falsified alprazolam).

An analysis of 197 trip reports from online forums, which describe use of clonazepam, was published. The reports mentioned hypnotic, amnesic and anxiolytic effects, with users rating clonazepam as having a short effect duration and a high potency score. This was consistent with predicted binding affinity based on QSAR models (El Balkhi et al., 2020; Waters et al., 2018).

Online forums describe clonazepam as a strong benzodiazepine and those who report recreational and nonmedical use note strong anxiolytic effects, tolerance, withdrawal and blackouts (Bluelight.org, 2020; Erowid.org, 2016). In discussions in these forums, clonazepam is considered one of the highest potency benzodiazepines, with a number of forum-users warning against its use due to its potency.

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

A study of samples of blood from intoxicated drivers from 2013 to 2016 identified seven samples containing clonazepam but none in which clonazepam was the sole intoxicant (Høiseth et al., 2016). In this study, clonazepam first appeared in early 2016 (Høiseth et al., 2016). The median concentration of clonazepam in blood was 0.0053 mg/L (range 0.0019–0.011 mg/L). A separate study of intoxicants examined samples from impaired drivers in Norway (between June 2016 and September 2019). In 22 of them, clonazepam was detected, but in no case was it the sole substance present, so impairment could not be specifically attributed to clonazepam (Heide et al., 2020). Of 6500 autopsy reports from this study, none identified clonazepam.

The propensity for clonazepam to potentiate the effects of alcohol and pentobarbital was demonstrated in preclinical studies, indicating that it is likely to contribute to overdose when combined with other sedative drugs (Hester et al., 1971).

The United Nations Office on Drugs and Crime (UNODC) Tox-Portal identified 29 reports involving clonazepam, all from the USA, during the period between 2017 and 2019. Around half of these cases involved driving under the influence of drugs, one was a postmortem analysis, and four were related to clinical admissions. These cases (20 of 29) mainly involved males, and 25 of the 29 cases involved clonazepam as the sole substance. Most ($n = 16$) cases were in people aged 15–24 years, while 11 reports involved people aged 25–44 years.

15. Licit production, consumption and international trade

Clonazepam was first synthesized in 1971 (Hester et al., 1971). No products were subsequently marketed, and no clinical trials of clonazepam have been registered. Clonazepam can currently be purchased from multiple chemical vendors.

16. Illicit manufacture and traffic and related information

A number of European and USA websites sell clonazepam in liquid, tablet, capsule, pellet or blotter form with prices for different preparations between 10 and 12 euro, or USD\$ 30 for a 30 mL vial. Bulk quantities are available from USA websites at higher prices (Murphy et al., 2019).

Domestic seizures of clonazepam have been reported in five states of the USA: Montana, Florida, Hawaii, Idaho and Texas (unpublished communication to WHO from the USA Drug Enforcement Administration, Diversion Control Intelligence Division). These cases involved clonazepam in falsified medicines, or products purchased from Internet sites (e.g. selling research chemicals) that were labelled as clonazepam.

Preliminary and incomplete data from USA law enforcement datasets indicate that clonazepam was involved in more than 570 independent seizure events domestically and/or at USA points of entry in 2019 and 2020 (Unpublished communication to WHO, 2020). The communication described this as a “dramatic increase” compared with previous years.

17. Current international controls and their impact

Clonazepam is not currently under international control.

18. Current and past national controls

Clonazepam is in Schedule 1 in Virginia (USA), Louisiana (Virginia Legislative Information System, 2020) and classified as a hazardous substance in Sweden (The Public Health Agency (Sweden), 2015).

In 2017 clonazepam was added to Schedule 2 of the Misuse of Drugs Act 1971 (United Kingdom Parliament, 2017). Clonazepam would be captured under a group listing for benzodiazepines as a Schedule IV substance in Canada (Government of Canada, 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 CLONAZOLAM

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, 36 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on CLONAZOLAM

Region	Number of countries without information	Number of countries with information on substance
Africa Region	12	4
Eastern Mediterranean Region	7	4
European Region	20	18
Region of the Americas	8	5
South-East Asia Region	5	1
Western Pacific Region	4	4
Total 92	56	36

LEGITIMATE USE

Four countries (two African Region, two Region of the Americas) reported approved human medical products or veterinary products containing CLONAZOLAM.

One country (Region of the Americas) reported CLONAZOLAM being currently used in medical or scientific research, “specifically in cell line studies (binding/functional assays) and animal studies”.

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

Four countries (two African Region, two Region of the Americas) reported approved therapeutic indications for CLONAZOLAM. These included:

- “Antiepileptics and anticonvulsants”
- “Benzodiazepines are commonly used for sedative, anxiolytic and amnestic effects in medical diagnostic and therapeutic procedures.”
- “Prevent and control seizure”
- “Treatment of certain seizure disorders of absence or Lennox–Gastaut syndrome, sleep inducer, anxiety crisis”.

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

Fifteen countries reported that CLONAZOLAM 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	12
Injection	0
Inhalation	0
Sniffing	1
Smoking	0
Don't know	20

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

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	7
Tablets	10
Liquid for oral use	3
Solution for injection	0
Don't know	19

To the above, countries added:

- capsules
- blotter paper
- stamp.

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

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

Serious	Substantial	Negligible	Don't know
5	4	8	17

One country (Western Pacific Region) noted, "The social harm caused by CLONAZOLAM is substantial". Another country (European Region) stated, "... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers, etc."

A third country (European Region) wrote, “Clonazepam is sometimes mixed in fake ‘street benzos’. There has been a small increase in the last year in the number of tablets containing it but numbers are still small. The first emergency room visits (two) have been reported recently.” Finally, one country (Region of the Americas) commented, “Clonazepam has been identified in an increasing number of law enforcement seizures and has contributed to at least two fatal and 19 non-fatal overdose events. It is abused by a broad range of groups, including youths, young adults and older adults.”

Five countries (four European Region, one Region of the Americas) reported emergency room admissions related to the non-medical use of CLONAZOLAM.

As for reported adverse effects, one country (European Region) noted “difficulty listing the side-effects associated with CLONAZOLAM because most often polyconsumption contexts”. Another country (Region of the Americas) reported, “Clonazepam has been identified in an increasing number of law enforcement seizures and has contributed to at least two fatal and 19 non-fatal overdose events. It is abused by a broad range of groups including youths, young adults and older adults.”. Finally, one country (European Region) reported the adverse side-effects as “fatigue and relatively low respiratory rate”.

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

Regarding mortality, only three countries (two European Region, one Region of the Americas) reported deaths involving CLONAZOLAM:

- one fatal case where other substances were also involved (2016)
- two fatal cases where it was unknown if other substances were involved (2018)
- one fatal case where this substance was the only substance involved (2019)
- two fatal cases where other substances were also involved (2019).

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

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

Table 5 shows the main reported activities involving CLONAZOLAM.

Table 5. Reported illicit activities involving CLONAZOLAM

Activities	Number of countries
Smuggling from other countries	4
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	5
Diversion from legal supply chain	1
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	4
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	2
Don't know	19

To the above, countries added:

- trafficking through postal services
- Internet sales (without other information).

Twelve countries provided information on seizures (Table 6).

Table 6. Reported seizures of CLONAZOLAM

Year	Seizures
2020	369
2019	848
2018	768
Total	1985

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

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