Critical Review Report:
FLUBROMAZOLAM

Expert Committee on Drug Dependence
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Executive summary

Flubromazolam is a novel or “designer” benzodiazepine that has never been subject to a clinical trial or registered for therapeutic use. Flubromazolam is a 1-4 triazolobenzodiazepine (similar to etizolam, triazolam and alprazolam) with a very high potency and long-lasting depressive effects on the central nervous system. The long half-life may increase the risk of harm and complicate clinical management compared with shorter acting benzodiazepines. Reflecting its high potency, doses of flubromazolam are typically low (0.15–0.40 mg) and it is usually taken orally as a liquid or tablet, although rectal, nasal, sublingual and inhaled routes of administration are also described. The effects of flubromazolam are reversed by the benzodiazepine antagonist flumazenil, although due to the long half-life of flubromazolam, patients can return to a comatose state when the effect of flumazenil wears off.

A single dose of 0.5 mg flubromazolam resulted in pharmacological effects (strong sedation and partial amnesia) lasting more than 24 hours, with reports on online forums and published case reports demonstrating that effects from a single dose can last several days.

No preclinical or clinical studies were found that describe abuse liability or dependence potential of flubromazolam, although reports from online sources describe severe withdrawal symptoms, loss of control over use and rapid onset of tolerance.

Limited information is available on the prevalence of use, and as flubromazolam is often consumed in falsified medicines it may often be consumed unintentionally. Nonmedical use of flubromazolam has been documented in multiple countries including Australia, Denmark, Norway, Poland, Sweden, the United States of America (USA) and Wales. Published reports of severe acute intoxication as well as fatal intoxication have appeared in recent years in these regions. Reports from online forums are consistent with scientific studies demonstrating high potency, amnesic and sedative effects, development of tolerance and severe withdrawal symptoms.

Flubromazolam is a controlled substance in Australia, Canada, Denmark, Finland, Sweden, Switzerland, Turkey, the United Arab Emirates, the United Kingdom and parts of the USA. It 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**
      612526-40-6
   C. **Other chemical names**
      8-bromo-6-(2-fluorophenyl)-1-methyl-4H-(1,2,4)triazolo(4,3-a)(1,4)benzodiazepine
      UNII-1BF1HN5GWD
      1BF1HN5GWD
      612526-40-6
      4H-(1,2,4)triazolo(4,3-a)(1,4)benzodiazepine, 8-bromo-6-(2-fluorophenyl)-1-methyl-
      SCHEMBL2841164
      DTXSID40620266
      VXGSZBZQCBNUIP-UHFFFAOYSA-N
      MFCD29036758
   D. **Trade names**
      None
   E. **Street names**
      liquid Xanax
   F. **Physical appearance**
      Flubromazolam is a white powder often sold as a liquid or as tablets (e.g. in falsified medicines). There are confirmed reports of flubromazolam being sold as alprazolam (Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS), 2019).
   G. **WHO review history**
      Flubromazolam has not been previously pre-reviewed or critically reviewed.

2. Chemistry
   A. **Chemical name**
      IUPAC Name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine
      CA Index Name: NA
B. Chemical structure

Flubromazolam is a 1-4 triazolobenzodiazepine, containing a fluorine, bromine and methylated triazole substituent on the benzodiazepine skeleton (Wohlfarth et al., 2017). The fluorine in the R2’ position leads to increased potency (El Balkhi et al., 2020).

\[
\text{Free base:}
\]

\[
\begin{align*}
\text{Molecular formula: } & C_{17}H_{12}BrF N_4 \\
\text{Molecular weight: } & 371.2
\end{align*}
\]

C. Stereoisomers

None

D. Methods and ease of illicit manufacturing

No information on the methods or ease with which flubromazolam is manufactured was identified, although methods for one-pot synthesis of triazolobenzodiazepines have recently been published (Ma et al., 2019).

E. Chemical properties

Melting point

Not found

Boiling point

520.6 ± 60.0 °C at 760 mmHg

Solubility

Flubromazolam is sparingly soluble in an aqueous buffer; it can be dissolved in dimethylformamide before dilution in an aqueous buffer, with a solubility of
0.5 mg/mL in a 1:1 dimethylformamide:phosphate buffered saline solution (Cayman Chemical, 2015).

F. Identification and analysis

Several publications report methods for the identification of flubromazolam. Flubromazolam is cross-reactive with a range of commonly used urine immunoassay tests (Pettersson Bergstrand et al., 2017). A series of samples from impaired drivers revealed challenges with immunoassays of blood. Negative blood benzodiazepine immunoassay responses were reported for six of seven cases, despite later confirmation of presence of flubromazolam by liquid chromatography–tandem mass spectrometry (LC–MS-MS) or gas chromatography-mass spectrometry (GC-MS) (Rohrig et al., 2020). This shows that some cases may be missed when screening with immunoassays. This is thought to be due to low concentrations of flubromazolam in blood which reflect the low doses of this high-potency benzodiazepine that are typically used (Rohrig et al., 2020).

The confirmation of flubromazolam in urine samples is described using LC–MS-MS by direct injection after enzymatic hydrolysis (Pettersson Bergstrand et al., 2016). This method identified flubromazolam in 96 patient samples out of 390 samples collected between Feb 2014 and Nov 2015 with a positive benzodiazepine immunoassay screen which tested negative for classical benzodiazepines. The flubromazolam a concentration range was 5.4–1500 ng/mL (Pettersson Bergstrand et al., 2016). LC–MS-MS has also been reported to detect flubromazolam in other biological samples, including serum, urine and hair (Huppertz et al., 2018). More sensitive LC-MS methods have been developed and validated using ultra-high-performance liquid chromatography (UHPLC) with a linear range of 0.5 to 1000 ng/mL, and a limit of detection for flubromazolam of 0.1 ng/mL (Tomková et al., 2017).

Novel LC–MS-MS methods have been developed to simultaneously identify and quantify flubromazolam and other novel benzodiazepines. They are able to identify flubromazolam in serum at concentrations between 5 and 600 ng/mL, with a limit of detection of 1.5 ng/mL (Švidrnoch et al., 2018). A validation study using postmortem blood samples demonstrated and validated use of LC–MS-MS to detect flubromazolam. This technique also identified flubromazolam (40 ng/mL) in a postmortem sample in which only etizolam and lorazepam had been identified initially using GC-MS. (Mei et al., 2019). Liquid chromatography high-resolution mass spectrometry (LC-HRMS) is also recommended as a sensitive method for identification of flubromazolam and other novel benzodiazepines (Pettersson Bergstrand et al., 2018a).

It was possible to detect a single dose in a hair sample 2 weeks after use of flubromazolam, which may useful in detecting substance use in drug-facilitated crimes (Huppertz et al., 2018).

Ultrahigh-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UHPLC-QTof) was used to test a drug sample of unconsumed pills identified as flubromazolam. This enabled subsequent identification of flubromazolam in the patient’s urine (Pope et al., 2018).
Flubromazolam metabolites have been detected using triple quadrupole mass spectrometry (El Balkhi et al., 2017). LC-HRMS has also been used to study human flubromazolam metabolism (Noble et al., 2017).

3. Ease of convertibility into controlled substances

No published information was available on the ease of convertibility of flubromazolam into controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Trip reports describe use of doses between 0.15 and 0.4 mg, with 0.35 mg being a common dose (El Balkhi et al., 2020; Moosmann and Auwärter, 2018). Administration has been reported via rectal, nasal, sublingual and intravenous routes (Andersson and Kjellgren, 2017). Smoking and use of vaporized flubromazolam are also described (Andersson and Kjellgren, 2017).

B. Pharmacokinetics

Consumption of a single 0.5 mg dose of flubromazolam was shown to lead to multiple peaks in serum concentration. The first peak was reached after 5 hours (7.4 ng/mL) and the second occurred after 8 hours (8.6 ng/mL, postprandial), possibly due to enterohepatic cycling of flubromazolam (Huppertz et al., 2018). The following day, sedative effects recurred, corresponding with a serum sample (30 hours post-intake) showing a repeated rise of the flubromazolam concentration to 5.2 ng/mL. Based on this single-participant study (with a single dose) a terminal elimination half-life of 10–20 hours was estimated. Reports from people who have taken flubromazolam describe an onset of action after 20–45 minutes, an average duration of effects of 3–6 hours and after-effects that last 1–14 hours (Zawilska and Wojcieszak, 2019). However, longer durations are described in online forums, for example, a study of reports from Sweden described effects lasting several days (Andersson and Kjellgren, 2017).

Metabolism of flubromazolam involves CYP3A4/5 and UGT1A4 enzymes (Noble et al., 2017; Pettersson Bergstrand et al., 2019), so enzyme polymorphisms may influence excretion and pharmacological effects. Major metabolites, formed predominantly by hydroxylation, dihydroxylation, and O-glucuronidation, include α-hydroxy-flubromazolam (the most abundant metabolite), 4-hydroxy-flubromazolam, flubromazolam N-glucuronide, α-hydroxy-flubromazolam glucuronide, and 4-hydroxy-flubromazolam glucuronide (Huppertz et al., 2018; Moosmann and Auwärter, 2018; Noble et al., 2017; Wohlfarth et al., 2017). Flubromazolam hydroxy metabolites have been suggested for use as target metabolites in urine (Pettersson Bergstrand et al., 2018b). Hepatic clearance of flubromazolam has been reported to be between 0.42 and 0.43 mL/min/kg (Noble et al., 2017). Flubromazolam is 89% plasma protein-bound (Manchester et al., 2018; Tomková et al., 2017).

Median blood concentrations of 0.012 mg/L (0.00048–0.10 mg/L) were reported for flubromazolam (n = 25) in a study of impaired drivers (Høiseth et al., 2016). Two cases involved only flubromazolam. In the first, the blood concentration was of 0.10 mg/L and
the driver was assessed as “considerably impaired”. In the second, the concentration was 0.00048 mg/L and the driver was assessed as mildly impaired. In a later study, median blood concentrations of 0.0056 mg/L flubromazolam (range 0.0004–0.0036 mg/L) were measured in 20 samples obtained predominantly from intoxicated drivers. However, none of these cases involved flubromazolam alone, meaning that the blood concentration associated with impairment could not be determined (Heide et al., 2020). One autopsy case from the same study reported a flubromazolam blood concentration of 0.052 mg/L.

C. Pharmacodynamics

A single 0.5 mg flubromazolam dose induced strong sedative effects that lasted more than 10 hours and partial amnesia over period of more than 24 hours (Huppertz et al., 2018). As with all benzodiazepines, flubromazolam achieves its pharmacological effect by allosterically potentiating chloride currents induced by gamma-aminobutyric acid (GABA) in GABA_A receptors.

5. Toxicology

No studies describing acute and preclinical toxicology were identified.

6. Adverse reactions in humans

Acute intoxication

The cases detailed below come from reports of acute nonfatal intoxication (n = 21), and fatal intoxication (n = 11) with flubromazolam. Patients commonly present in severely drowsy or comatose states, often with protracted symptoms related to the long half-life of flubromazolam. The benzodiazepine antagonist flumanzenil is used to manage acute symptoms in some cases (Bäckberg et al., 2019). However, if long-term benzodiazepine use is likely to increase the risk of withdrawal and seizures, or a patient is on other proconvulsant medications, flumazenil may not be used owing to seizure risk (Bohnenberger and Liu, 2019). Patients who have taken flubromazolam have been admitted to intensive or critical care units, with effects lasting 8–24 hours or more (Carpenter et al., 2019).

Australia

- A 32-year-old man in treatment for opioid dependence (taking methadone, 50 mg daily) 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 score of 10. An initial screening of his urine for drugs was positive for benzodiazepines, and further investigation identified doxylamine, clonidine, oxazepam, temazepam, methadone and a methadone metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), which were felt did not explain the presentation. Additional analysis using UHPLC-QToF revealed that the pills contained 16 mg of clonazolam and 0.18 mg of flubromazolam. Flubromazolam was subsequently detected in the patient’s urine.
The patient was discharged after 15 days of hospitalization including a lengthy stay in intensive care.

Poland

- A 27-year-old man was found in a comatose state, with urinalysis showing that benzodiazepines were involved (Łukasik-Głębocka et al., 2016). Toxicological analysis detected flubromazolam (59 ng/mL in the serum and 105 ng/mL in the urine). The patient improved following administration of the benzodiazepine antagonist flumazenil (1.0 mg for about 30 minutes), before returning to the previous state thus confirming the involvement of benzodiazepines. The patient was mechanically ventilated for 4 days and transferred to the neurology department after 9 days. The severe and long-lasting central nervous system depression with cardiorespiratory failure and brain hypoxic-ischaemic changes was attributed to an estimated dose of 3.0 mg (0.043 mg/kg body weight).

Sweden

- Seventeen cases in which presence of flubromazolam in the urine was confirmed were described. In 15 of these cases, flubromazolam was the only benzodiazepine involved, and 2 of them involved flubromazolam with meclonazepam (Bäckberg et al., 2019). Most of the cases concerned younger people (from 17 years old), although the age range extended to 65 years old. Several cases required admission to an intensive care unit for up to 72 hours. Common symptoms included central nervous system depression, drowsiness, disorientation, slurred speech, hypotension, and both dilated pupils and miotic pupils (Bäckberg et al., 2019). In each case the presence of flubromazolam was confirmed in the urine, usually after an initial positive screening for benzodiazepines. Flumazenil (0.1–0.6 mg) was administered in seven cases and a response to flumazenil was documented in all patients to whom it was administered. In this report covering a range of novel benzodiazepines, flubromazolam was identified as both the most prevalent and the most hazardous.

United Kingdom

- A 25-year-old male was reported to have been mute and apparently having visual hallucinations prior to loss of consciousness in his home, with later seizures during his hospital admission (Dickenson and Keohane, 2015). He had a history of mental health conditions and had been prescribed analgesia for back pain. He reported use of flubromazolam (purchased online from China), in addition to oxycodone, ketamine, cannabis and possible heroin. His urine tested positive for benzodiazepines (consistent with self-reported flubromazolam use) and cannabis, although confirmatory toxicology was not described in the report.

United States

- A 36-year-old male with a history of mental health conditions and substance use disorder experienced prolonged bradycardia following use of 0.4 mg flubromazolam purchased from the Internet to self-manage his anxiety (Bohnenberger and Liu, 2019). He was monitored in intensive care and treated with supportive fluids before
being transferred for management of his sedative dependence. Flumazenil was not administered due to risks of seizure given the patient’s long-term benzodiazepine use and concurrent proconvulsant medications. Benzodiazepines were detected in routine screening of urine for drugs, although further confirmatory testing was not described in the report.

Deaths

Denmark
- Analysis of two unrelated forensic samples (case one was a 41-year-old man, and case two was a 47-year-old man), identified flubromazolam in addition to a range of other pharmaceuticals and substances (Noble et al., 2017). Methadone intoxication was recorded as the cause of death in both cases. The concentration of flubromazolam in femoral blood in case one was 0.0080 mg/kg and that in case two was 0.0044 mg/kg.

United Kingdom
- The Advisory Council on the Misuse of Drugs reported a death in 2015 in which flubromazolam was implicated in the cause of death (Iverson, 2016). No further details on the death were reported.

United States of America
- A 24-year-old male who took flubromazolam (purchased online and mailed to him while he was an inpatient in a treatment facility for substance use disorder) died. His death was attributed to complications of overdose after an extended hospital stay (Gummin et al., 2017). His urine tested positive for benzodiazepines, although further confirmatory testing for flubromazolam was not described in the report. Flumazenil was administered but the patient did not respond to this treatment.
- An autopsy report on a 34-year-old male with a history of depression and suicidal ideation who was found dead in his home, revealed the presence of 3-FPM, flubromazolam, U47700, delorazepam, amitriptyline, nortriptyline, methamfetamine, amfetamine, diazepam, nordiazepam and temazepam in the femoral blood as well as 3-FPM in the urine (Ellefsen et al., 2017). Death was attributed to accidental multiple drug toxicity (diazepam, U-47700, temazepam, flubromazolam, delorazepam, methamfetamine, 3-FPM and amitriptyline).

7. Dependence potential

A. Animal studies
No animal studies on the dependence potential of flubromazolam were identified.

B. Human studies
No human studies on the dependence potential of flubromazolam were identified. Reports by people who use flubromazolam describe severe withdrawal symptoms, loss of control over use and rapid onset of tolerance (Andersson and Kjellgren, 2017).
8. Abuse potential
   
   A. Animal studies
   
   No animal studies on abuse potential of flubromazolam were identified.
   
   B. Human studies
   
   No human studies on abuse potential of flubromazolam were identified.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use
   
   No therapeutic applications of flubromazolam were identified.

10. Listing on the WHO Model List of Essential Medicines
    
    Flubromazolam is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)
    
    Flubromazolam does not have any marketing authorizations as a medicinal product.

12. Industrial use
    
    None identified.

13. Nonmedical use, abuse and dependence
    
    Nonmedical use of flubromazolam is documented in multiple countries including Australia, Denmark, Norway, Poland, Sweden, the USA and Wales, although limited data on the prevalence of use are available.

    The USA National Poisons Data System reported 13 cases of single-agent flubromazolam poisoning in 2016 (n = 2) and 2017 (n = 11). It is therefore less common in single-agent exposure than etizolam (n = 106 cases over the same time period) (Carpenter et al., 2019). Poisonings typically involved younger males (85% males, median age 24 years, range 18–36 years), with most cases representing acute exposure (77%) in the context of “abuse” (77%) (Carpenter et al., 2019).

    The Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS) has published details of more than 70 samples in which flubromazolam was the main drug detected (Welsh Emerging Drugs & Identification of Novel Substance Project (WEDINOS), 2020). These reports, published between 2015 and 2020, confirmed the presence of flubromazolam in the samples tested. In recent years almost all flubromazolam was sold as falsified medicines (most often as diazepam and less often as alprazolam or zolpidem). This is in contrast to samples tested in earlier years, which tended to be sold as “reagents” packaged with warnings such as “not for human use”. One sample that tested positive for flubromazolam through the WEDINOS programme, which was sold as Xanax®, also contained MDMB-4en-PINACA.

    An analysis of 197 trip reports from online forums was published, describing use of flubromazolam, commonly ingested as a liquid and associated with a long duration of effects (El Balkhi et al., 2020). The main effects were hypnosis and amnesia, which were
reported more often than anxiolytic and euphoric effects. Of the 10 novel benzodiazepines examined, flubromazolam scored equal second-highest for potency. The high potency score is consistent with predicted binding affinity based on quantitative structure–activity relationship models (El Balkhi et al., 2020; Waters et al., 2018).

The first reported seizure associated with flubromazolam in Sweden occurred in September 2014 (Bäckberg et al., 2019). The Swedish Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser (STRIDA) study identified 92 confirmed cases involving flubromazolam intoxication in Sweden, making it the most prevalent novel benzodiazepine in the report. Clinical data were available for 24 cases where intoxication with novel benzodiazepines was analytically confirmed. Of these, 15 cases involved flubromazolam as the only benzodiazepine. Most cases were detected in late 2014 and in 2015.

In its second quarter 2020 report, the US Center for Forensic Science Research and Education described eight cases in which flubromazolam use was detected. These included forensic samples from case types linked to illicit drug investigations, medicolegal death investigations, and/or investigations of driving under the influence of drugs (Krotulski et al., 2020).

Findings from 52 nonfatal cases of acute intoxication with 3-MeO-PCP and/or 4-MeO-PCP (collected between 2013 and 2015) were analysed as part of the STRIDA project (Bäckberg et al., 2015). Co-intoxication with flubromazolam was identified in five of these cases.

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

Reports from an online forum in Sweden from people who use flubromazolam describe the withdrawal syndrome associated with flubromazolam as more severe than with other benzodiazepines. They mention rapid development of tolerance, and “worse and longer” withdrawal symptoms including muscle aches, sleeping disorders, panic attacks, dissociative symptoms, perceptual distortions, cramping, vomiting and seizures (Andersson and Kjellgren, 2017).

Cases of impaired driving associated with flubromazolam have been reported. It was the most commonly detected novel benzodiazepine in a study of samples from impaired drivers in Norway (between July 2013 and May 2016) (Høiseth et al., 2016). A later study (June 2016 – September 2019), however, found that flubromazolam was no longer commonly detected relative to other novel benzodiazepines (Heide et al., 2020).

A US study of 12 drivers stopped because of impaired driving identified flubromazolam in 9 of them (Rohrig et al., 2020). The mean blood concentration of flubromazolam was 16.3 ng/mL (range 7.0–31 ng/mL). The drivers were typically young (17–35 years old), and had consumed multiple substances, including cannabis and cocaine.

The United Nations Office on Drugs and Crime (UNODC) Tox-Portal identified 129 reports involving flubromazolam. Most (n = 103) cases involved driving under the influence of drugs; 20 were postmortem reports; and 5 related to clinical admissions. Most reports involved males (n = 107) and mainly involved people aged 15–24 years (n = 48) and 35–44
years \( (n = 31) \). Most reports were from the USA \( (n = 113) \) with 14 from Canada, one from Finland and one from the United Kingdom.

The National Board of Forensic Medicine in Sweden identified 41 autopsy cases which had been confirmed to involve flubromazolam, and 27 nonfatal cases from contexts such as traffic incidents, violent crimes or probation control in which flubromazolam consumption was confirmed (Wohlfarth et al., 2017).

The long half-life of flubromazolam may contribute to overdose when it is combined with other drugs such as opioids. This may also make the drug prone to accumulation with repeated dosing, which may also contribute to overdose risk (Huppertz et al., 2018). People who use flubromazolam substances may not be aware of these risks.

Characteristics of flubromazolam such as its high potency and its potential to cause strong sedation and amnesia at low oral doses are thought to increase its potential danger. This is due to challenges in measuring doses from bulk materials, and also the potential for its use in drug-facilitated crimes (Moosmann et al., 2015).

15. **Licit production, consumption and international trade**

Flubromazolam is currently sold online as a research chemical.

16. **Illicit manufacture and traffic and related information**

No descriptions of illicit manufacture of flubromazolam were found. However, Moosmann & Auwärter (2018) explained that the synthesis of triazolo-analogues such as flubromazolam is feasible with available 1,4-benzodiazepines, and that a large number of doses of flubromazolam can be made from a given amount of 1,4-benzodiazepines with relatively low synthesis effort.

17. **Current international controls and their impact**

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

18. **Current and past national controls**

Schedule 1 in Virginia USA (Virginia Legislatitive Information System, 2020).

In 2017, flubromazolam was added to Schedule 2 of the Misuse of Drugs Act 1971 (United Kingdom Parliament, 2017).

Flubromazolam would be captured under a group listing for benzodiazepines as a Schedule IV substance in Canada (Government of Canada, 2020).

Flubromazolam is under international control in Denmark, Finland, Sweden, Switzerland, Turkey, and the United Arab Emirates (Zawilska and Wojcieszak, 2019).

Flubromazolam was captured under a group benzodiazepine Schedule 4 (prescription only) listing in Australia. The Australian Therapeutic Goods Administration up-scheduled it to Schedule 9, which came into effect in 2016 (Therapeutic Goods Administration (TGA), 2015). The decision was based on the assessment that flubromazolam has no therapeutic use, carries risks of undetected “spiking” due to the low doses required, has a high
potential for nonmedical use and a risk of overdose, and that local attempts to illegally import the drug had resulted in seizures.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance
None
References


Manchester KR, Maskell PD, Waters L (2018). Experimental versus theoretical log D(7.4), pK(a) and plasma protein binding values for benzodiazepines appearing as new psychoactive substances. Drug testing and analysis. doi:10.1002/dta.2387


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

Table 1. Numbers of countries providing information on FLUBROMAZOLAM

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of countries without information</th>
<th>Number of countries with information on substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa Region</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>European Region</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total 92</strong></td>
<td><strong>58</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

LEGITIMATE USE

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

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

One country (Region of the Americas) reported FLUBROMAZOLAM being used in industrial or other non-medical or non-scientific use.

One country (Region of the Americas) reported therapeutic indications approved for FLUBROMAZOLAM. “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 FLUBROMAZOLAM 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**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>7</td>
</tr>
<tr>
<td>Injection</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation</td>
<td>0</td>
</tr>
<tr>
<td>Sniffing</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>21</td>
</tr>
</tbody>
</table>

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

**Table 3. Common formulations reported by countries**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>4</td>
</tr>
<tr>
<td>Tablets</td>
<td>7</td>
</tr>
<tr>
<td>Liquid for oral use</td>
<td>1</td>
</tr>
<tr>
<td>Solution for injection</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>19</td>
</tr>
</tbody>
</table>

To the above, countries added:
- blotter paper (blue)
- trips.

Eight countries reported the level of negative health-impact due to FLUBROMAZOLAM’s non-medical consumption as “serious” or “substantial” (Table 4).

**Table 4. Level of negative health-impact**

<table>
<thead>
<tr>
<th></th>
<th>Serious</th>
<th>Substantial</th>
<th>Negligible</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

One country (European Region) stated, “… there may be unknown cases of negative health impacts because … there is no reporting obligation by hospitals, poison centers, etc.”. Another (European Region) added, “Flubromazolam 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 (5) have been reported recently”. A third country (Region of the Americas) reported, “Flubromazolam has been identified in an increasing number of law enforcement seizures. It is abused by a broad range of groups including youths, young adults and older adults. In 2018 FLUBROMAZOLAM was identified by law enforcement in driving under the [influence]…”.

Four countries (three European Region, one Region of the Americas) reported emergency room admissions related to the non-medical use of FLUBROMAZOLAM.
As for reported adverse effects, one country (European Region) commented, "In combination with other drugs: reduced conscience, meiosis, bradycardia, tachycardia, hypertension, agitation, confusion". Another country (European Region) noted, "Addiction. Difficulty naming side effects attributed to FLUBROMAZOLAM because context of polyconsumption (opioids, benzodiazepines in particular)".

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

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

- two fatal cases where other substances were also involved (2017)
- one fatal case where other substances were also involved (2020).

**STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL**

Sixteen countries responded that FLUBROMAZOLAM is currently controlled under national legislation to regulate its availability.
Table 5 shows the main reported activities involving FLUBROMAZOLAM.

Table 5. Reported illicit activities involving FLUBROMAZOLAM

<table>
<thead>
<tr>
<th>Activities</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smuggling from other countries</td>
<td>2</td>
</tr>
<tr>
<td>Manufacture of substance by chemical synthesis</td>
<td>1</td>
</tr>
<tr>
<td>Manufacture of substance by extraction from other products</td>
<td>0</td>
</tr>
<tr>
<td>Production of consumer products containing the substance</td>
<td>0</td>
</tr>
<tr>
<td>Trafficking</td>
<td>6</td>
</tr>
<tr>
<td>Diversion from legal supply chain</td>
<td>0</td>
</tr>
<tr>
<td>Internet sales – seller or website located in country</td>
<td>1</td>
</tr>
<tr>
<td>Internet sales – from abroad to buyers in country</td>
<td>3</td>
</tr>
<tr>
<td>Internet sales – other, or location of sellers and website unknown</td>
<td>4</td>
</tr>
<tr>
<td>Direct sales to people who use the substance</td>
<td>2</td>
</tr>
<tr>
<td>Don’t know</td>
<td>18</td>
</tr>
</tbody>
</table>

To the above, countries added:
- trafficking through postal services
- Internet sales without other information.

Eleven countries reported non-zero numbers of seizures (Table 6).

Table 6. Reported seizures of FLUBROMAZOLAM

<table>
<thead>
<tr>
<th>Year</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>58</td>
</tr>
<tr>
<td>2019</td>
<td>390</td>
</tr>
<tr>
<td>2018</td>
<td>477</td>
</tr>
<tr>
<td>Total</td>
<td>925</td>
</tr>
</tbody>
</table>

Twenty-six countries have the forensic laboratory capacity to analyse FLUBROMAZOLAM.

One country (European Region) noted, “Forensic laboratories have the capacity to analyse FLUBROMAZOLAM if reference material is available”. 