Critical review report:
Bromazolam

Expert Committee on Drug Dependence
Forty-fifth Meeting
Geneva, 10–14 October 2022

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Executive summary

Bromazolam (Chemical Abstracts Service [CAS] registry number: 71368-80-4; CAS name: 8-bromo-1-methyl-6-phenyl-4H-S-triazolo[4,3-a][1,4]benzodiazepine) is a triazolobenzodiazepine that was originally developed as a candidate medication but was never approved for use. The first documented detection of bromazolam by government authorities was in Sweden in 2016. Since then, the compound has been detected in products or in biological samples in nine countries: Australia, Austria, China, Finland, Germany, India, Sweden, the United Kingdom (Wales) and the USA. Bromazolam is not under international control. It is classified in schedule IV under Canadian law and is controlled under psychoactive drug regulations in Germany and the United Kingdom.

Little information on bromazolam is available in the scientific literature. Online forum posts suggest that the primary route of administration is oral (tablets, capsules, solutions and “gummies”); however, in one fatality, it was detected analytically in two syringes next to the body. Informational websites for users list a dosage range according to intoxicating effects: “light” (0.5–1 mg), “common” (1–2 mg) and “strong” (2–4 mg). Onset of effects after oral use is estimated to be 15–45 min, and the duration of action is 5–8 h.

Bromazolam phase I metabolism is mediated primarily by several isoforms of the CYP450 enzyme system (CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9), whereas phase II metabolism involves the isoenzymes UGT1A4 and UGT2B10. Monohydroxylated metabolites include 4-hydroxylated bromazolam and α-hydroxy bromazolam, with an additional dehydroxylated metabolite, α-5-dihydroxy-bromazolam. After glucuronidation, α-hydroxy glucuronide and N-glucuronide are the most abundant phase II metabolites. Information on the compound’s pharmacodynamics is confined to a single in-vitro study of its binding to α subunits of the γ-aminobutyric acid type A/benzodiazepine receptor complex. Bromazolam was non-selective for α subunits, showing measurable binding affinity at receptors containing α1 (Ki = 2.8 nM), α2 (Ki = 0.69 nM) and α5 (Ki = 0.62 nM) subunits.

Bromazolam in post-mortem blood samples has been confirmed analytically in Finland and the USA. In the USA, it was detected in over 250 toxicology cases (2020 to the present), 236 post-mortem and 14 cases of driving impairment. The rate of detection increased from 1% to its current 13%, and co-detection with fentanyl in recent months increased to 75%. The causality of bromazolam in the deaths and other adverse effects could not be assigned definitively, as toxicological results often showed use of more than one substance. Bromazolam-containing tablets have appeared on the illicit market labelled as a legal benzodiazepine (e.g., as falsified alprazolam and diazepam products).

The primary source of information about its psychological effects is self-reports in online forum by people who have used bromazolam. The reasons given for its use include intentionally seeking psychoactive effects and self-medication (e.g., anxiety, sleep-inducing or modulation of a stimulant effect). The reported effects of intentional use include “hypnotic” and “sedative” sensations. Other reports describe muscle relaxation and analgesia; some people have reported amnesia. Online forum posts of self-reported use of bromazolam should be considered anecdotal, as there was no analytical confirmation of sole use of bromazolam.
1. Substance identification
   A. International nonproprietary name
      Not assigned
   B. Chemical Abstracts Service registry number
      71368-80-4
   C. Other chemical names
      8-Bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine
      8-Bromo-1-methyl-6-phenyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine
      DE(chloro)-bromo-alprazolam
   D. Trade names
      Bromazolam is sold under its own name.
   E. Street names
      Bromazolam is sold as tablets or powders under its own name or as XLI-268 (1).
      Novel psychoactive substances belonging to the benzodiazepines class can be purchased mainly on the drug online market under various street names, such as “legal benzodiazepines”, “designer benzodiazepines” and “research chemicals” (2).
   F. Physical appearance
      Synthetic bromazolam has been described as a white solid (3) or a crystalline solid (4).
   G. WHO review history
      Bromazolam has not been reviewed previously by the WHO Expert Committee on Drug Dependence.

2. Chemistry
   A. Chemical name
      IUPAC name:
      8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-α][1,4]benzodiazepine
      Chemical Abstracts Service index name:
      4H-[1,2,4]Triazolo[4,3-α][1,4]benzodiazepine, 8-bromo-1-methyl-6-phenyl- (9CI, ACI)
   B. Chemical structure
      Free base:
Molecular formula: \( \text{C}_{17}\text{H}_{13}\text{BrN}_4 \)
Molecular weight: 353.22 g/mol

C. Stereoisomers

No stereoisomers of bromazolam have been described.

D. Methods and ease of illicit manufacture

Bromazolam is a triazolo-benzodiazepine structurally related to the internationally controlled substance alprazolam in which the chlorine atom is replaced by a bromine atom. Bromazolam is also structurally related to flubromazepam, from which it differs by the lack of a fluorine at the 2-position of the phenyl ring. Bromazolam is also structurally similar to pyrazolam, whereby the pyridinyl group has been replaced by a phenyl group (3).

Bromazolam was first synthesized in the 1970s by Hester et al. (5). A convenient synthesis method has been reported in the patent literature (3, 6, 7). Introduction of a triazole ring into the 1,4-benzodiazepine precursor (8-bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine) gave bromazolam. The 1,4 benzodiazepine precursor can be prepared by cyclization of 2-amino-5-bromobenzophenone with chloroacetylchloride (scheme 1) (8).

Scheme 1. Synthesis of bromazolam

No information was available about the routes of synthesis used for the bromazolam products circulating on the market. The synthesis reported in the literature, although simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point
272.0–275 °C (3, 5)

Boiling-point
No information was found.

**Solubility**

Bromazolam is soluble in dimethylformamide at a concentration of 30 mg/mL, in dimethylsulphoxide at 20 mg/mL, in ethanol at 10 mg/mL, in methanol at 1 mg/mL and in a 1:1 mixture of dimethylformamide and phosphate-buffered saline (pH 7.2) at 0.5 mg/mL (4).

**F. Identification and analysis**

Synthetic bromazolam has been characterized by proton and carbon nuclear magnetic resonance (1H NMR and 13C NMR), mass spectrometry (MS) and infra-red spectroscopy (IR) (3). Bromazolam is available as a reference material from various commercial suppliers and is used in routine analysis for forensic and clinical investigations (3).

Analytical methods for identification of bromazolam in seized sample matrices include IR, 1H NMR, gas chromatography–MS and liquid chromatography–MS (9, 10).

Bromazolam was also analysed in urine in an immunochemical assay (11) and in human blood and urine by LC coupled either to high-resolution MS or to triple–quadrupole MS (9, 10, 12).

3. **Ease of conversion into controlled substances**

No information was found.

4. **General pharmacology**

A. **Routes of administration and dosage**

Seizures by law enforcement personnel indicate that bromazolam is typically formulated in tablets or as a powder (1). Oral use (e.g., tablets, capsules or powder formulations in solutions or mixed in food) has been reported on online forums (13–16). Bromazolam-containing chewable candy products (“gummies”) have also been seen (15). While injection is assumed from the presence of a syringe filled with bromazolam-containing solution found next to an overdose victim (1), this route of administration does not appear to be common.

No studies were found of human dosage; however, one informational website has categorized doses according to their intoxicating effects as “light” (0.5–1 mg), “common” (1–2 mg) and “strong” (2–≥ 4 mg) (17). For comparison, the website lists the following doses for diazepam: “light” (2.5–5 mg), “common” (5–15 mg) and “heavy” (15–30 mg) (18). A review of novel psychoactive benzodiazepines listed 1 mg as a “typical recreational dose” (19). The onset of effects is estimated to occur 15–45 min after administration, the duration of action is 5–8 h, and the after-effects last 1–12 h (17). The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting these data.

B. **Pharmacokinetics**

In the only study available, the pharmacokinetics of bromazolam was studied in pooled human liver S9 fractions, with further analysis of authentic blood and urine samples from two patients (20). The primary metabolic reactions were hydroxylation, glucuronidation and combinations of the two processes, resulting in eight metabolites. Two prominent monohydroxylated metabolites were formed, tentatively identified as 4-hydroxylated bromazolam and α-hydroxy bromazolam, as well as one dehydroxylated metabolite, α-4-dihydroxy-bromazolam.
Glucuronidation resulted in \( \alpha \)-hydroxy glucuronide and \( N \)-glucuronide as the most abundant phase II metabolites. The parent compound was detected in the urine of both patients, whereas the monohydroxylated metabolites were detected in only one. Recommended screening targets in urine were \( \alpha \)-hydroxy glucuronide and \( N \)-glucuronide if conjugate cleavage was performed or the parent compound and the \( \alpha \)-hydroxy metabolite if it was not. Isoenzymes involved in phase I metabolism included CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9, whereas phase II metabolism involved the isoenzymes UGT1A4 and UGT2B10.

C. Pharmacodynamics

Little information was found on the pharmacodynamics of bromazolam. It has not been evaluated empirically in vivo. Bromazolam was tested in a single in-vitro study of the binding of several compounds (including bromazolam) to \( \alpha \) subunits of the \( \gamma \)-aminobutyric acid type A (GABA\( \alpha \)) / benzodiazepine receptor complex (21). Affinity for compounds in HEK cell membranes expressing recombinant GABA\( \alpha \)/benzodiazepine receptor subtypes (\( \alpha 1\beta 3\gamma 2\), \( \alpha 2\beta 3\gamma 2\), \( \alpha 3\beta 3\gamma 2\), \( \alpha 4\beta 3\gamma 2\), \( \alpha 5\beta 3\gamma 2\) and \( \alpha 6\beta 3\gamma 2\) was measured. Bromazolam was non-selective for the \( \alpha \) subunits, with measurable binding affinity at receptors containing \( \alpha 1\) (\( K_i = 2.8 \) nM), \( \alpha 2\) (\( K_i = 0.69 \) nM) and \( \alpha 5\) (\( K_i = 0.62 \) nM) subunits.

5. Toxicology

No studies of the preclinical toxicology of bromazolam were available.

6. Adverse reactions in humans

The presence of measurable concentrations of bromazolam in post-mortem blood samples has been reported in Finland and the USA (1, 22); however, other drugs were also detected in many cases, and the extent to which bromazolam contributed to the deaths was not specified. In Germany, two patients with confirmed bromazolam use were found unconscious or minimally responsive (20). Bromazolam has also been reported in blood samples from impaired drivers in the USA (22). The reports do not provide details of the physical or behavioural effects of bromazolam use.

People who used bromazolam described its effects as “hypnotic” and “sedative” (13) and referred to its “muscle relaxing” and “pain relieving” properties (15). Other reported effects include euphoria, increased confidence, and empathy (23). Some people who used bromazolam reported amnesia, while others stated that amnesia was less common with bromazolam than with other benzodiazepines (16). Posts on online forums describing self-reported experience of use of bromazolam should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.
8. Abuse potential
   
   A. *Studies in experimental animals*
      No information was found.
   
   B. *Studies in humans*
      No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use
   
   There are no known therapeutic uses for bromazolam.

10. Listing on the WHO Model Lists of Essential Medicines
    
    Bromazolam is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)
    
    Bromazolam has no known marketing authorizations.

12. Industrial use
    
    Bromazolam has no known industrial use.

13. Non-medical use, abuse and dependence
    
    Bromazolam appeared on the European recreational drug market in 2016 in Sweden and in the USA in 2019 (22, 24). In addition to intentional use of bromazolam for its benzodiazepine-like psychoactive effects (see section 6), some people have reported self-medication with bromazolam for indications such as anxiety, to aid sleep and to reduce stimulation caused by another drug such as methamphetamine (15, 16). Bromazolam has been detected in formulations that contain combinations of benzodiazepines in a single preparation (e.g., tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g., alprazolam, diazepam, zolpidem) (23, 25). The compound has been used in combination with other drugs, including fentanyl and other opioids (15, 22).

    The prevalence of chronic use and dependence of bromazolam has not been reported. On online forums, several people have reported difficulty in withdrawing from bromazolam after chronic use, and at least one case of withdrawal-associated psychosis and hallucinations was reported after bromazolam was taken repeatedly in combination with phenibut (26–28). These reports should be considered anecdotal, as no analytical confirmation of bromazolam (or its sole use) was reported.
14. **Nature and magnitude of public health problems related to misuse, abuse and dependence**

Little information is available on fatal and non-fatal poisonings with analytically confirmed use of bromazolam. In Finland, bromazolam was found in a post-mortem blood sample with other benzodiazepines (1). In Germany, bromazolam was present in biological samples from two patients, one of whom was found unconscious and one of whom was “confused and slow to respond” (20). In the USA, bromazolam has been analytically confirmed in more than 250 cases, with 236 detections in post-mortem blood and 14 in biological samples from impaired drivers (22). While no additional information was available on the clinical course of the cases or on any other drugs present, the average bromazolam blood concentration in post-mortem samples was 65 ng/mL (± 79 standard deviation) (22). In samples from impaired drivers, the average blood concentration was 61 ng/mL (± 47 standard deviation) (22). Between October 2020 and February 2022, 10 cases (seven post-mortem) of analytically confirmed bromazolam were reported by the USA to the Early Warning System Tox-Portal (29). In all cases, bromazolam was designated as contributory (medium) on the causality scale used in the system. Bromazolam was the only substance detected in half of the cases. In 2022, bromazolam was the sole (or one of only a few) substance(s) detected in over 200 samples analysed by Welsh authorities (23). A substantial number of products were falsely labelled as an approved prescription benzodiazepine (e.g., diazepam, alprazolam, zolpidem).

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

No information was found.

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

The first documented seizure of bromazolam in Europe was in Sweden in 2016 (24), while reports in the USA first appeared in 2019 (22). In the USA, its detection increased from 1% of samples in the first quarter of 2021 to 13% in the second quarter of 2022 (22). Its detection with fentanyl has increased dramatically, with 75% of bromazolam-positive samples also containing fentanyl in the months before the report was issued in June 2022 (22). Samples containing bromazolam submitted to an anonymous testing site (from 2020 to the present) were received from Austria (n=1), China and other Asian countries (n=5), India (n=1), the United Kingdom (n=1) and the USA (n=27) (30). As submission of samples was voluntary, the distribution of sites of origin may not represent the distribution or trafficking of bromazolam in the world. Other countries in which bromazolam has been detected include Australia (25), Finland (1), Germany (20), Sweden (24) and Wales (23).

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

Bromazolam is not currently under international control.

18. **Current and past national controls**

Bromazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. It does not appear to be controlled under national regulations in other countries.
19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No information was found.

References


