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Distributed to:

Chief Executives
Directors of Clinical Governance
Director, Regulation and Compliance Unit

Action required by:

Chief Executives
Directors of Clinical Governance

We recommend you also inform:

Directors, Managers and Staff of:

- Drug and Alcohol Services
- Mental Health Services
- Emergency Departments
- Toxicology Units
- Pharmacy
- Ambulance

Expert Reference Group

Content reviewed by:

- Centre for Alcohol and Other Drugs, NSW Ministry of Health
- Standing Panel on Toxicity Risk
- Chief Pharmacist

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UPDATED: Composition of counterfeit alprazolam in NSW

What's new in this Safety Information?

Novel benzodiazepines are being seen increasingly in toxicology testing of drug-related hospitalisations. This Safety Information supersedes **SI:006/22** and provides updates on the increasing variety of novel benzodiazepines and other substances detected in samples of counterfeit alprazolam, including multiple benzodiazepines in one tablet. Some tablets contain no benzodiazepines at all, so patients may potentially present in withdrawal, even whilst taking counterfeit alprazolam.

Figure 1. Counterfeit alprazolam products reported by NSW Health clinicians. Note 'Kalma' is an Australian registered brand of alprazolam and it may be difficult to differentiate between legitimate and counterfeit products.



Background

NSW Health last issued a public drug warning in August 2022 regarding counterfeit alprazolam – available [here](#).

Since this warning was issued, an increasing number of novel benzodiazepines and a small number of other substances have been detected in counterfeit alprazolam products. This Safety Information provides an update on these detections to July 2023 based on analysis of drug composition of samples seized by NSW Police and those associated with clinical cases in NSW.

Assessment

Since 2019, there have been ongoing detections of counterfeit alprazolam products containing an increasing variety of novel benzodiazepines from police seizures. Novel benzodiazepines are being seen increasingly from toxicology testing of drug-related hospitalisations in the Prescription, Recreational and Illicit Substance Evaluation (PRISE). Counterfeit alprazolam products are often poorly manufactured, with a wide variation in the drug composition. Up to five different benzodiazepines have been detected in a single tablet associated with some hospitalisations. Large dose variations in the benzodiazepines detected have been found between visually similar counterfeit tablets in the same batch,¹ although some counterfeit tablets have been found to have variable thickness. Novel benzodiazepines have been associated with serious harm and death in NSW. Dependence and withdrawal are significant concerns with use and the variable drug composition increases this risk as 3% have no benzodiazepines present.

Counterfeit alprazolam products have tablet markings or packaging resembling "Kalma", "Mylan", "Xanax", "Sandoz" or "Alprax" (examples in Figure 1 above). "Mylan" and "Xanax" make up most of counterfeit alprazolam products seen. Neither are registered products in Australia. 2 mg products make up almost all products seen.

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Only 7% of counterfeit alprazolam samples analysed contained alprazolam, and all of these were found to also contain other substances. The other substances detected were mostly novel benzodiazepines, with a small number of samples containing other drugs.

Twelve novel benzodiazepines have been detected to date in NSW: etizolam, clonazolam, bromazolam, flualprazolam, flubromazepam, deschloroetizolam, bromonordiazepam (desalkygidazepam), flubromazolam, phenazolam, phenazepam, adinazolam, and diclazepam. 7% of samples had other substances detected – etodesnitazene (a strong opioid), desmethyltramadol, doxepin, clozapine, paracetamol, caffeine, 1,4-butanediol, lidocaine, amantadine, cyproheptadine, promethazine, the stimulants methamphetamine, N-ethyl heptedrone, N-(1, 4-dimethylpentyl)-3,4-DMA and the hallucinogens dimethyltryptamine and 5-methoxy-DBT.

A larger range of novel benzodiazepines are being detected in counterfeit alprazolam than previously reported in 2019 and 2020. There is also a change in the novel benzodiazepines most commonly detected. In 2019, etizolam was the most commonly detected substance, however this has now shifted to other novel benzodiazepines, notably bromazolam and clonazolam (see Figure 2 below). Bromazolam has also become the predominant novel benzodiazepine detected overseas.²

Figure 2. Proportion of substance detections in counterfeit alprazolam products from January 2019 to July 2023.



Clinical Recommendations

1. Be aware that if a patient is taking illicitly obtained alprazolam or has Xanax or Mylan alprazolam tablets, the product most probably contains other novel benzodiazepines. They often contain multiple benzodiazepines and variable strength compared to registered medicines. Rarely, they may contain other drug classes with variable toxicity.

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2. Take caution when interpreting urine drug screen (UDS) results if a novel benzodiazepine is suspected. Some novel benzodiazepines are detected by UDS but may not be able to be identified on confirmatory testing. Misinterpretation as a false positive has been reported.³ Additionally, some novel benzodiazepines may not be detected on initial UDS. Consult your local pathology service if results appear incongruent with suspected illicit benzodiazepine use and/or confirmatory testing is required.
3. If the patient has significant clinical signs such as central nervous system and respiratory depression, seizures, and/or ECG changes, provide standard emergency care and consult your local toxicologist or the Poisons Information Centre on 13 11 26, who can advise on further management and arrange specific testing as indicated.

References

1. Blakey K, Thompson A, Matheson A, Griffiths A. What's in fake 'Xanax'? A dosage survey of designer benzodiazepines in counterfeit pharmaceutical tablets. *Drug Test Anal.* 2022;14(3):525-530. doi:10.1002/dta.3119, 10.1002/dta.3119
2. Krotulski, AJ; Walton, SE; Mohr, ALA; Logan, BK. (2023) NPS Discovery Q3 2023 Trend Reports, Center for Forensic Science Research and Education, United States.
3. Puzyrenko A, Wang D, Schneider R, Wallace G, Schreiber S, Brandt K, Gunsolus IL, Urine drug screening in the era of designer benzodiazepines: Comparison of three immunoassay platforms, LC-QTOF-MS and LC-MS/MS. *J Anal Toxicol.* 2021; bkab108, <https://doi.org/10.1093/jat/bkab108>

Required actions for the Local Health Districts/Networks

1. Instruct clinicians to be alert for continued circulation of counterfeit alprazolam products and be vigilant during patient histories which report use of alprazolam or other benzodiazepines and the interpretation of urine drug screen results if illicit benzodiazepine use is suspected. Clinicians should consider referral to toxicology or the Poisons Information Centre on 13 11 26 if the patient has significant clinical signs.

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