EUDA
EUROPEAN UNION DRUGS AGENCY

EU Early Warning System: Formal Notification

Formal notification of 2-{[4-(2-fluoroethoxy)phenyl]methyl}-5-nitro-1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-1,3-benzimidazole (fluetonitazepyne) by Italy as a new psychoactive substance under the terms of Regulation (EU) No 2023/1322 and Council Framework Decision 2004/757/JHA

Date issued	**RCS ID**
16.09.2024	EU-EWS-RCS-FN-2024-0031
Issued by	**Transmitted by**
EUDA	Action on New Drugs Sector, EUDA

1. Read me first

This document provides formal notification of the analytical identification of 2-{[4-(2-fluoroethoxy)phenyl]methyl}-5-nitro-1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-1,3-benzimidazole (fluetonitazepyne) for the first time in Europe.

Please report any additional data you have on this substance to: ews@euda.europa.eu

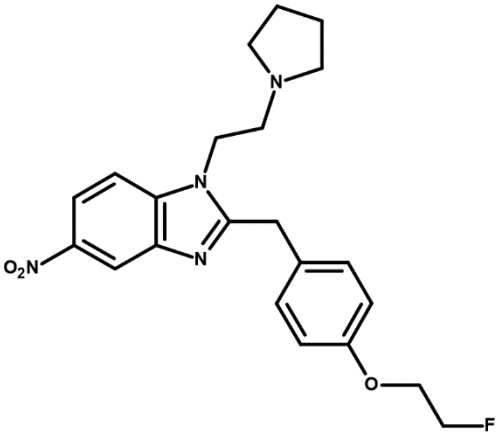
2. Data use restrictions

As with all formal notifications issued by the EU Early Warning System (EWS), remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this notification to other groups we would ask that you exercise your best judgment on what information needs to be provided. If you have any questions in this respect, please contact us.

3. Names of substance and other identifiers

- **IUPAC name:** 2-{[4-(2-fluoroethoxy)phenyl]methyl}-5-nitro-1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-1,3-benzimidazole
- **Chemical names:** 2-[[4-(2-fluoroethoxy)phenyl]methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)benzimidazole; 2-(4-(2-fluoroethoxy)benzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzo[*d*]imidazole
- **Common name:** Fluetonitazepyne
- **Other names:** F-etonitazepyne; fluoro-etonitazepyne; *N*-pyrrolidino fluetonitazene; *N*-pyrrolidino-4'(2-fluoroethoxy) nitazene
- **Chemical formula:** $C_{22}H_{25}FN_4O_3$
- **Molecular weight:** 412.45
- **CAS Registry number:** not registered
- **InChIKey:** TYLHUWCBBIQCEH-UHFFFAOYSA-N

Molecular structure:



4. Substance classification

Opioid

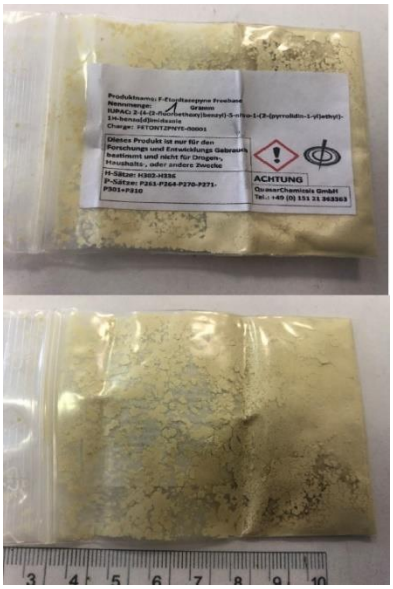
5. Detection

Type: Seizure

Case Report identifier: EDND-CR-2024-845

Details: fluetonitazepyne (fluoro-etonitazepyne, F-etonitazepyne) was identified in 0.725 grams of flaky yellow powder inside an airtight bag, seized on 25 July 2024 by Italian Police (Carabinieri). The product was labelled as “F-Etonitazepyne Freebase” and shipped from Germany.

Fluetonitazepyne was analytically confirmed by HRMS, Raman and FTIR by the Reparto Investigazioni Scientifiche Carabinieri di Roma. NMR analysis was also conducted.



Other detections

Type: Collected sample

Case Report identifier: EDND-CR-2024-878

Details: fluetonitazepyne was also identified in 500 milligrams of yellow powder in a test purchase conducted by the EU-project NETZWERK ADEBAR [1], on 27 July 2024 and collected by the University Medical Center Freiburg, Institute of Forensic Medicine, Forensic Toxicology Department.

Fluetonitazepyne was analytically confirmed using GC-MS, (HR)-LC-MS, GC-sIR, ATR-IR, FT-NIR, Raman and NMR by the EU-project NETZWERK ADEBAR. The free base form of fluenitazepyne was identified in the collected sample.

6. Chemistry and Analysis

Chemical classification: azacyclic; azole; benzimidazole

Fluetonitazepyne, a 5-nitro-2-benzylbenzimidazole is the fluorinated analogue of the internationally controlled substance etonitazepyne (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs). Fluetonitazepyne differs from etonitazepyne by the replacement of the ethoxy in the *para*-position at the benzyl moiety by a fluoroethoxy group.

Fluetonitazepyne also shares structural similarities with other 5-nitro-2-benzylbenzimidazole opioids under intensive monitoring by the EU EWS, such as protonitazepyne (formally notified in July 2023) and metonitazepyne (formally notified in October 2023). Both protonitazepyne and metonitazepyne have recently been the focus of critical review reports [2,3] by the World Health Organisation's Expert Committee on Drug Dependence (ECDD) and will be critically reviewed by the ECDD on 14 -18 October 2024.

A reference standard is available for fluetonitazepyne citrate which is reported to be sparingly soluble in DMSO (1-10 mg/ml) [4]

7. Pharmacology and toxicology

Pharmacological classification: opioid

There is no information available on the pharmacology and toxicology of fluetonitazepyne. Based on its chemical structure and on its similarity to etonitazepyne and etonitazene, fluetonitazepyne is expected to have opioid narcotic analgesic effects.

Similarly, to other opioids that share the 2-benzylbenzimidazole core structure, fluetonitazepyne is expected to be a selective μ opioid receptor (MOR) antagonist. A recent *in vitro* study reported the structure-activity relationship of 2-benzimidazole opioids but the effect on the substitution of the ethoxy with a fluoroethoxy group has not been yet accessed [5].

8. Further information

Further information on this substance is available on the EDND profile:
https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1539

9. Acknowledgements

The Italian National Focal Point, Italian Police (Carabinieri), Reparto Investigazioni Scientifiche Carabinieri di Roma, the German National Focal Point, Bavarian State Police State Bureau of Criminal Investigation Schleswig-Holstein, the University Medical Center Freiburg, Institute of Forensic Medicine, Forensic Toxicology Department, and EU-project NETZWERK ADEBAR are kindly acknowledged for the information and analytical data provided.

10. Attachments

None.

11. References

[1] Pulver B, et al. The ADEBAR project: European and international provision of analytical data from structure elucidation and analytical characterization of NPS. Drug Test Anal.2022;14(8):1491-1502.

[2] https://cdn.who.int/media/docs/default-source/controlled-substances/47th-ecdd/n-pyrrolidino-protonitazene-47th-ecdd-critical-review-public-version.pdf?sfvrsn=1d210d9_2

[3] https://cdn.who.int/media/docs/default-source/controlled-substances/47th-ecdd/n-pyrrolidino-metonitazene-47th-ecdd-critical-review-public-version.pdf?sfvrsn=47344eae_2

[4] https://www.caymanchem.com/product/41221/n-pyrrolidino-fluetonitazene-(citrate)

[5] De Vrieze L, et al. In vitro structure-activity relationships and forensic case series of emerging 2-benzylbenzimidazole ‘nitazene’ opioids. Arch Toxicology. 2024;98:2999-3018