European Monitoring Centre for Drugs and Drug Addiction

EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	14 May 2024	RCS ID	EU-EWS-RCS-FN-2024-0011
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of *N*,*N*-diethyl-2-[2-[[4-(2-fluoroethoxy)phenyl]methyl]-5-nitro-benzimidazol-1-yl]ethanamine (fluetonitazene) by Germany as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA		

1. Read me first

This document provides formal notification of the analytical identification of *N*,*N*-diethyl-2-[2-[[4-(2-fluoroethoxy)phenyl]methyl]-5-nitro-benzimidazol-1-yl]ethanamine (fluetonitazene) for the first time in Europe.

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

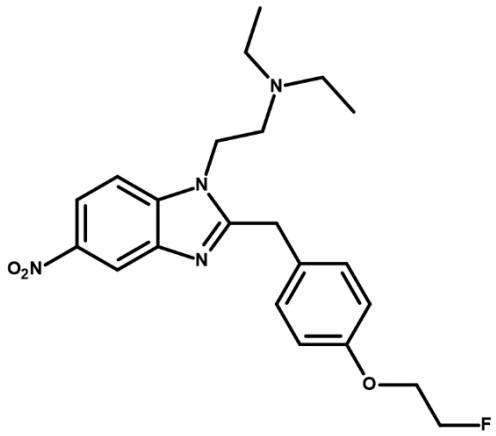
2. Data use restrictions

As with all formal notifications issued by the EU 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: *N*,*N*-diethyl-2-[2-[[4-(2-fluoroethoxy)phenyl]methyl]-5-nitro-benzimidazol-1-yl]ethanamine
- Chemical names: *N*,*N*-diethyl-2-(2-(4-(2-fluoroethoxy)benzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine; *N*,*N*-diethyl-2-(2-{[4-(2-fluoroethoxy)phenyl]methyl}-5-nitro-1*H*-1,3-benzimidazol-1-yl)ethan-1-amine
- Common name: fluetonitazene
- Other names: F-Etonitazene; F-Eto; 2F-Eto; 2F-Etonitazene; Fluoro-Etonitazene; 4'-(2-fluoroethoxy) nitazene
- Chemical formula: $C_{22}H_{27}FN_4O_3$
- Molecular weight: 414.47
- CAS number: not available
- InChIKey: XCWWXPKOMYPTRP-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Opioid

5. Detection

Type: Collected sample
Case Report identifier: EDND-CR-2024-378

Details: fluetonitazene was identified in a test-purchase of one millilitre of e-liquid contained in a vial, collected by the University Medical Center Freiburg, Institute of Forensic Medicine, Forensic Toxicology Department, on 29 March 2024.

The substance was analytically confirmed using GC-MS, GC-sIR, and NMR by the EU-funded project NETZWERK ADEBAR. The sample was reported to contain unidentified impurities.

6. Chemistry and Analysis

Chemical classification: azacyclic; azole; benzimidazole

Fluetonitazene, a 5-nitro-2-benzylbenzimidazole and also known as F-Etonitazene, is a fluorinated analog of the internationally controlled substances etonitazene, metonitazene and protonitazene (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs), where ethoxy, methoxy and propoxy are replaced with fluoroethoxy in the *para*-substitution at the benzyl moiety.

Fluetonitazene is structurally related to the internationally controlled isotonitazene and clonitazene (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs), differing due to the replacement of fluoroethoxy in the *para*-substitution at the benzyl moiety with isopropoxy and chlorine, respectively.

Fluetonitazene also shares structural similarities to the 5-nitro-2-benzylbenzimidazoles fluonitazene (flunitazene), butonitazene and ethyleneoxynitazene, formally notified in 2020, 2021 and 2023, respectively. The substances differ from fluetonitazene in the *para*-substituent at the benzyl moiety, where fluoroethoxy is replaced with fluorine, butoxy and tetrahydrofuran in fluonitazene, butonitazene and ethyleneoxynitazene, respectively.

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

According to Quasar Chemicals, a freezing point of - 60 °C and a boiling point of 188 °C have been reported for the hydrochloride salt of fluetonitazene [2].

7. Pharmacology and toxicology

Pharmacological classification: opioid

Information on the pharmacology and toxicology of fluetonitazene is limited. Based on its chemical structure and on its similarity to etonitazene, metonitazene and protonitazene, fluetonitazene is expected to have opioid narcotic analgesic effects.

The μ-opioid receptor (MOR) activity of protonitazene and 13 other nitazenes, has been evaluated using two *in vitro* recruitment assays (MOR-βarr2 and MOR-mini-Gi) [2]. All the nitazene compounds were found to be active at MOR, with protonitazene in the group of nitazenes with a potency found to be 1.5−10 times higher than that of fentanyl [3]. In the study, the authors noted that the *para*-ethoxy substituent (etonitazene) yielded the highest potency in both assays, followed by -isopropoxy (isotonitazene), -propoxy (protonitazene), -methoxy (metonitazene), and -butoxy (butonitazene) [3]. They also highlighted that the results indicated that either a “relatively short (ethoxy) or more compact (isopropoxy) alkoxy tail is optimal for MOR activation” [3]. Additionally, the study highlighted that the replacement of the *para*-alkoxy tail with a chlorine or fluorine halogen was associated with a “drastically decreased potency relative to isotonitazene” [3]. In a mouse tail-flick assay, clonitazene exhibited potency 3 times greater than morphine, whereas flunitazene demonstrated antinociceptive potency similar to that of morphine [3].

During the mid-1950s, attempts to develop better and safer opioid analgesics led to the discovery of a series of 2-benzylbenzimidazole compounds with levels of analgesic potency several orders of magnitude higher than that of morphine.

Similar to other types of opioid analgesics such as morphine and fentanyl, the 2-benzylbenzimidazole compounds activate the μ-opioid receptors in the central nervous system. It is expected that the effects of such compounds are likely to share similarities with fentanyl and other opioid analgesics. The acute effects include: euphoria, relaxation, analgesia (a reduced ability to feel pain), sedation (inducing a state of calm or sleep), bradycardia (slowing of the heart), hypothermia (dangerously low body temperature), and respiratory depression (slowing down of breathing). It is this latter effect that poses the greatest danger to users, as, due to the apparently high potency of some of these compounds, small amounts may cause life-threatening poisoning from respiratory depression. Left untreated, this can lead to respiratory arrest (stopping breathing) and death. This risk can be exacerbated by the use of other central nervous system depressants.

The timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics. Although the available information is limited, and, similarly to other opioid analgesics, 2-benzylbenzimidazole opioids are likely to have an abuse liability and dependence potential.

8. Further information

Further information on this substance is available on the EDND profile:
https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1497

9. Acknowledgements

The German National Focal Point, State Police Schleswig-Holstein, the EU-funded project NETZWERK ADEBAR and the University Medical Center Freiburg, Institute of Forensic Medicine, Forensic Toxicology Department are kindly acknowledged for the information and analytical data provided.

10. Attachments

None.

11. References

[1] https://www.caymanchem.com/product/40834/fluetonitazene-(citrate)
[2] https://quasar-chemicals.com/produkt/f-etonitazene-liquid-1mg-pro-ml/
[3] Vandeputte MM, et al. Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of “Nitazene” 2-Benzylbenzimidazole Synthetic Opioids. ACS Chemical Neuroscience. 2021;12(7):1241-51