World Health Organization

Critical review report

Etonitazepipne

(*N*-piperidinyl etonitazene)

Expert Committee on Drug Dependence

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Executive summary

Etonitazepipne (also known as *N*-piperidinyl etonitazene) is one of several synthetic 2-benzylbenzimidazoles opioids, collectively known as “nitazenes”. While etonitazepipne was initially developed as an opioid analgesic in the late 1950s, it was never submitted for regulatory approval or brought to the legal drug market. In 2021, etonitazepipne emerged on the illicit drug market in Europe and in the USA. By the end of 2022, the presence of this substance had been reported in at least six countries (Austria, Canada, Germany, Italy, the United Kingdom and the USA). While etonitazepipne is not under international control, it is regulated under national psychoactive drug control regulations in Italy, the United Kingdom and the USA and has been placed under intensive monitoring in the European Union.

The available data, including reports from people who use etonitazepipne and law enforcement seizures, indicate that it is usually purchased in powder form. The most common route of administration is insufflation after solubilization into a nasal spray. Secondary routes include intravenous, oral and inhalation of vapour after heating. While information on dosage is sparse, online reports from people who self-report use of etonitazepipne list doses in intranasal sprays of 75–100 μg per spray, with three to six sprays per use. Given the anecdotal nature of this information, caution is suggested in its interpretation.

After administration, etonitazepipne undergoes extensive hepatic phase-I biotransformation, including *O*-dealkylation, hydroxylation, oxidation and combinations of these processes. Etonitazepipne binds with high affinity to the μ opiate receptor (MOR) and was more than 1000 times more selective for the MOR than for the κ and Δ opioid receptors. Etonitazepipne is a full agonist at the MOR, as measured in several functional in-vitro assays. It induced potent analgesic, cataleptic and hypothermic effects in rodents. In rats, etonitazepipne produced morphine-like discriminative stimulus effects that were reversible by co-administration of naltrexone. The potency of etonitazepipne was intermediate between those of morphine and fentanyl, the efficacy of the three compounds being approximately equal. These results indicate that etonitazepipne would have subjective effects in humans similar to those of morphine and other MOR agonists.

The presence of measurable concentrations of etonitazepipne in post-mortem blood samples and in biological samples from people admitted clinically has been reported by several sources. Fourteen deaths have been reported in three countries. In some cases, other drugs were also detected (including other opioids); however, etonitazepipne was the only substance detected in at least two fatalities in which the probability of causality in the deaths was considered high. Clinical admissions associated with etonitazepipne presented with low levels of consciousness and respiratory depression. These symptoms were reversible by administration of naloxone.

Etonitazepipne has been reported in Europe and North America. While etonitazepipne is banned and/or under increased surveillance in the European Union and in several other countries, accurate estimates of its prevalence and traffic have been complicated by its rapid appearance on the illicit market, underreporting due to initial lack of reference standards and its high potency (requiring measurement of minute amounts in forensic samples).

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1. Substance identification

A International Nonproprietary Name (INN)

Not available.

B Chemical Abstracts Service (CAS) Registry Number

734496-28-7

C Other chemical names

2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)benzimidazole
2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazole
1*H*-Benzimidazole, 2-((4-ethoxyphenyl)methyl)-5-nitro-1-(2-(1-piperidinyl)ethyl)-
2-((4-Ethoxybenzyl)-5-nitro-1-(2-(1-piperidinyl)ethyl)-1*H*-benzimidazole

D Trade names

Etonitazepipne is sold as an analytical standard as citrate salt under the name "*N*-piperidinyl etonitazene (citrate)" *(1).*

E Street names

Etonitazepipne is known under its own name or as *N*-piperidinyl etonitazene.

F Physical appearance

Etonitazepipne citrate as a reference material has been described as a crystalline solid *(1).* Etonitazepipne hydrochloride has been described as a white-yellowish powder *(2)*. A sample of etonitazepipne obtained from an online supplier has been described as a yellow homogeneous powder *(3).*

G WHO review history

Etonitazepipne has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name
2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole

CA Index name
1*H*-Benzimidazole,2-[(4-ethoxyphenyl)methyl]-5-nitro-1-[2-(1-piperidinyl)ethyl]

Canonical SMILES

O=N(=O)C=1C=CC2=C(N=C(N2CCN3CCCCC3)CC4=CC=C(OCC)C=C4)C1

InChI

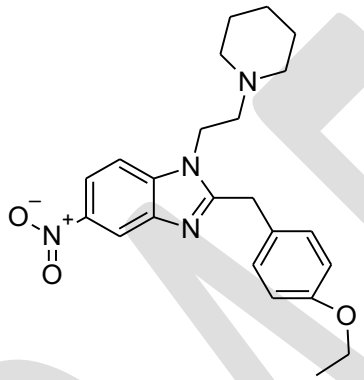
1S/C23H28N4O3/c1-2-30-20-9-6-18(7-10-20)16-23-24-21-17-19(27(28)29)8-11-22(21)26(23)15-14-25-12-4-3-5-13-25/h6-11,17H,2-5,12-16H2,1H3

InChI key

UMGXRAISFRUVKD-UHFFFAOYSA-N

B *Chemical structure*

Free base:



Molecular formula: $C_{23}H_{28}N_4O_3$
Molecular weight: 408.49 g/mol

C *Stereoisomers*

No stereoisomers have been described for etonitazepipne.

D *Methods and ease of illicit manufacture*

Etonitazepipne belongs to the opioid 2-benzylbenzimidazoles group, also known as "nitazenes", which were initially developed as opioid analgesics in the late 1950s *(4)*. Etonitazepipne closely resembles etonitazepyne but has a piperidino ring instead of a pyrrolidino ring at the 1-position of the benzimidazole ring *(2,5)*.

Synthesis of etonitazepipne was reported by Hunger et al. *(6)*. The activated chloro atom of 1-chloro-2,4-dinitrobenzene can easily be substituted by 1-(2-aminoethyl)piperidine. Then, regioselective reduction of the nitro group in the ortho position to the resulting amino function and condensation of the ortho-phenylenediamine species with ethoxyphenyl imidate (obtained from ethoxyphenylacetonitrile derivative) results in the 5-nitro-substituted final product etonitazepipne. It is possible to obtain etonitazepipne through other synthetic routes with the methods established for 5-nitro-2-benzylbenzimidazole analogues, with appropriate modifications to the reagents *(5,7–10)*.

While no details of the production method or the scale of the recently identified etonitazepipne are available, the synthesis techniques used for its nitazene analogues suggest that the process is straightforward, cost-effective and does not require regulated precursors.

E Chemical properties

Melting-point: 181–184 °C (Etonitazepipne hydrochloride) *(6)*

Boiling-point: No information could be identified

Solubility: Etonitazepipne is soluble in dimethylformamide (DMF) and in dimethyl sulfoxide (DMSO) 10 mg/mL. In PBS (pH 7.2), it is soluble at 1 mg/mL *(1).*

F Identification and analysis

Etonitazepipne citrate is available as reference material from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(1)*.

Analytical methods for the identification of etonitazepipne in seized sample matrices include liquid chromatography high-resolution mass spectrometry (LC-HRMS), gas chromatography–mass spectrometry (GC–MS), LC-diode array detector and Fourier-transform infrared *(2)*.

LC-HRMS analytical methods were developed to quantify etonitazepipne in serum *(2,11)* and urine *(2)* and to identify its principal urinary metabolites *(2)* in patients suspected of opioid overdose.

An LC-HRMS method was developed to identify and quantify etonitazepipne in post-mortem biological matrices such as urine, gastric content and vitreous humour *(12),* and an LC–tandem MS method was developed to quantify etonitazepipne in post-mortem blood and urine *(13)*.

3. Ease of conversion into controlled substances

No information was available in the literature about whether etonitazepipne can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

The literature and user reports suggest that etonitazepipne is most commonly administered by insufflation after solubilization into a nasal spray *(2,14,15)*. Intravenous administration may also be used, as syringes containing etonitazepipne were found near two decedents in cases of overdose *(16).* Less commonly

mentioned routes of administration include oral and inhalation of vapour after heating *(15,17)*.

Dosage estimates are based entirely on self-reports from people who use it. The reported doses delivered in intranasal sprays are 75–100 μg per spray, with three to six sprays per usage *(2,14,15)*. These anecdotal data should be interpreted with caution.

B Pharmacokinetics

No studies were identified on the absorption, distribution or elimination of etonitazepipne. Its metabolism was studied in vitro (in pooled human liver microsomes) *(2)* and in vivo (in biological samples) *(13)*. The parent compound was found in serum and urine samples at levels of 1.21–7.4 ng/mL and 0.51–6.9 ng/mL, respectively. Phase-I metabolic transformation included *O*-dealkylation, hydroxylation, oxidation and combinations of these processes. Whether these metabolites are psychoactive has not been assessed in vivo; however, *N*-piperidinyl 4'-OH nitazene (the hypothetical primary metabolite) was 11 and 21 times less potent than etonitazepipne in β-arrestin 2 recruitment (EC_{50} = 56.9 nM) and cyclic adenosine monophosphate (cAMP) (EC_{50} = 4.75 nM) functional assays *(18)*. These results suggest that the metabolites of etonitazepipne could retain psychoactivity, albeit at reduced potency than the parent compound (see also see comment in *2*).

C Pharmacodynamics

Etonitazepipne binds with high affinity to the MOR. The K_i for displacement of [^{3}H] [D-Ala^2, *N*-MePhe^4, Gly-ol]-enkephalin ranged from 0.51 ± 0.10 nM *(19)* to 14.3 ± 2.5 nM *(2)*. In comparison, the MOR K_i for fentanyl was 1.255 ± 0.084 nM to 6.17 ± 0.82 nM in the same two studies, respectively. Etonitazepipne showed over 1000 times more selectivity for the MOR than for the κ opioid (K_i = 1290 ± 110 nM) and Δ (Ki = 607 ± 63 nM) opioid receptors *(19)*.

Like fentanyl, etonitazepipne is a full, potent agonist at MOR, as measured in a [^{35}S]GTPγS assay (EC_{50} = 8.47 ± 0.81 nM; E_{max} = 98.4 ± 6.7%) *(19)*. In contrast, it had low potency for activation of the κ and Δ opioid receptors (EC_{50} = 1610 ± 370 nM and 2370 ± 3.1 nM, respectively). Replicate in-vitro assays verified that etonitazepipne is a full agonist for enhancement of β-arrestin 2 recruitment, with EC_{50} values ranging from 3.06 nM (95% confidence interval: 2.19 ; 4.26 nM) *(2)* to 5.12 nM (95% confidence interval: 3.5 ; 7.4 nM) *(18)* and inhibition of forskolin-stimulated cAMP, with EC_{50} = 0.222 nM (95% confidence interval: 0.157 ; 0.319 nM) *(18)*.

In rats treated subcutaneously, etonitazepipne had potent analgesic effects in a hot-plate assay (ED_{50} = 0.0205 mg/kg) *(2)*. In this assay, it was approximately equipotent with fentanyl (fentanyl ED_{50} = 0.0209 mg/kg). The peak effect occurred at a dose of 0.1 mg/kg 15 min after administration. Etonitazepipne also produced analgesic effects in mice, which were reversible with naltrexone (see Annex 3 for details). In rats treated subcutaneously, etonitazepipne also induced catalepsy (ED_{50}

= 0.0354 mg/kg) and a pronounced, sustained drop in body temperature at a dose of 0.10 mg/kg *(2)*.

5. Toxicology

No studies of the preclinical toxicology of etonitazepipne were found.

6. Adverse reactions in humans

The presence of measurable concentrations of etonitazepipne in 14 post-mortem biological samples was reported in Germany (n=1), Italy (n=3) and the USA (n=10) *(12,13,16,20,21)*; however, the presence of other drugs, including other opioids, was also reported in many of these cases. The extent to which etonitazepipne was causal to or contributed to the deaths was not specified in most instances. In two cases (one in Germany and one in Italy), etonitazepipne was considered to be the primary cause of death *(12,13,20)*. In 2021, three patients admitted to the emergency department of a New Jersey (USA) hospital tested positive for etonitazepipne *(11,22)*. All three patients were found unresponsive before admission and showed respiratory depression upon arrival at hospital. Treatment with naloxone resolved the clinical signs of opioid intoxication. Analysis of biological samples from two patients showed the presence of other opioids, whereas only etonitazepipne was reported in the third.

The predominant effects of etonitazepipne described by people who have used it include euphoria, relaxation, itchiness, energetic feelings and slight nodding or sedation *(14,15)*. Posts on online forums on self-reported experience of use of etonitazepipne 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 animals

Drug discrimination is a pharmacologically selective animal model of the subjective effects of psychoactive drugs in humans. Etonitazepipne produced full dose-dependent substitution in rats trained to discriminate morphine from vehicle. These effects were reversed by naltrexone. See Annex 3 for additional details.

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 of etonitazepipne.

10. Listing on the WHO Model List of Essential Medicines

Etonitazepipne is not listed on the 23rd WHO Model List of Essential Medicines or on the 9th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Etonitazepipne has no known marketing authorization.

12. Industrial use

Etonitazepine has no known industrial use.

13. Non-medical use, abuse and dependence

Etonitazepipne was first synthesized in the 1950s during development of a medication by CIBA Aktiengesellschaft in Switzerland; however, it was not submitted for regulatory approval or brought to the legal drug market. In 2021, etonitazepipne emerged on the illicit synthetic drug market in Europe and the USA *(23)*. Reports on online forums by people who use drugs provide evidence that etonitazepipne has been used intentionally for its intoxicating effects (see section 6). By the end of 2022, the presence of this substance had been reported in at least six countries (see section 16 for listing). The prevalence of chronic use and dependence of etonitazepipne has not been reported.

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

Since its emergence as a novel psychoactive substance in 2021, etonitazepipne has been analytically confirmed in post-mortem samples and in samples collected from patients admitted to emergency departments in several countries, including Germany, Italy and the USA. Between 2021 and 2023, 10 cases of analytically confirmed etonitazepipne were found post-mortem in the USA *(16,24)*. In each case, other psychoactive substances (including other opioids) were present in the biological samples, and some decedents had comorbid conditions that may have compromised their health. Hence, a definitive statement about the extent to which etonitazepipne caused or contributed to death could not made in any of the cases. Three additional fatalities occurred in Italy between July and September 2022 *(12,20)*. Whereas the cause of death in two of the cases could not be attributed definitively to etonitazepipne due to the presence of cocaine and other opioids in biological samples, etonitazepipne was considered to be the primary cause of death in the third fatality *(12,20)*. Etonitazepipne overdose was also identified as the primary cause of death of an individual in

Germany in 2022 *(13)*. In this case, the concentration of etonitazepipne in femoral blood was 8.3 ng/mL.

Nonfatal cases of etonitazepipne use have also been reported. Etonitazepipne was analytically confirmed in the serum of three patients who presented to the emergency department of a hospital in New Jersey (USA) *(11,22)*. In all three cases, the individuals had been found nonresponsive and had respiratory depression or low oxygen saturation upon admission. The symptoms of all the patient resolved with administration of naloxone *(22)*. As biological samples from two of the patients also contained other psychoactive substances, including other opioids, the clinical symptoms could not be attributed solely to etonitazepipne. The third patient tested positive only for etonitazepipne, suggesting that the clinical signs were related to overdose of this compound.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

Countries in which the presence of etonitazepipne has been reported are Austria, Canada, Italy, Germany, the United Kingdom and the USA *(13,20,24,25)*. While etonitazepipne is banned and/or under increased surveillance in the European Union and in several countries (e.g. Canada, the United Kingdom and the USA), accurate estimates of its prevalence and traffic have been complicated by its rapid appearance on the illicit market, its high potency (requiring measurement of minute amounts in forensic samples) and underreporting due to an initial lack of reference standards *(23)*.

17. Current international controls and their impact

Etonitazepipne is not currently under international control.

18. Current and past national controls

In 2023, an order for temporary placement of etonitazepipne under schedule 1 of the US Controlled Substances Act was published *(23)*. Benzimidazoles and their derivatives are also classified under Schedule 1 under Canadian law. In the United Kingdom, etonitazepipne was included in the list of new Class A substances issued in 2023 *(25)*. In 2022, etonitazepipne was placed under intensive monitoring in the European Union *(13)*, and it was included in Table 1 of narcotic drugs issued by the Italian Ministry of Health *(20)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

None

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