



EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	26 June 2020	RCS ID	EU-EWS-RCS-FN-2020-0017
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of <i>N,N</i> -diethyl-2-[2-[(4-methoxyphenyl)methyl]benzimidazol-1-yl]ethanamine (metodesnitazene) by Belgium as a new psychoactive substance under the terms of Regulation (EU) 2017/2101		

1. Read me first

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

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

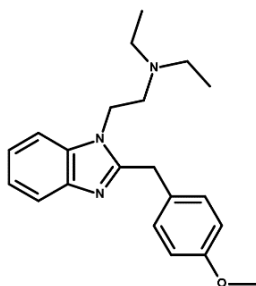
2. Data use restrictions

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-methoxyphenyl)methyl]benzimidazol-1-yl]ethanamine
- Chemical names: *N,N*-diethyl-2-(2-(4-methoxybenzyl)-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine; *N,N*-diethyl-2-[2-(4-methoxybenzyl)-1*H*-benzimidazol-1-yl]ethanamine; *N,N*-diethyl-2-{2-[(4-methoxyphenyl)methyl]-1*H*-benzimidazol-1-yl}ethan-1-amine; 1-(2-(diethylamino)ethyl)-2-(*p*-methoxybenzyl)-benzimidazole; diethyl-[2-[2-(4-methoxybenzyl)benzimidazol-1-yl]ethyl]amine; 1-(2-diethylaminoethyl)-2-(*p*-methoxybenzyl)benzimidazole; 2-(*p*-anisyl)-1-(2-diethylaminoethyl)benzimidazole
- Common name: metodesnitazene
- Other names: BRN 0765000; NSC 659139
- Chemical formula: C₂₁H₂₇N₃O
- Molecular weight: 337.46
- CAS Registry number: 14030-77-4 (base); 1071546-40-1 (hydrochloride salt)
- InChIKey: SFNKTTXBZXVGOH-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Opioid

5. Detection

Type: collected sample

Case Report identifier: EDND-CR-2020-458

Details: metodesnitazene was identified in 1 gram of white powder, collected by the Belgian Early Warning System Drugs (BEWSD) from an internet site (surface web), on 1 May 2020. The substance was contained in a plastic bag and the product name was observed to be 'metodesnitazene'.

The substance was analytically confirmed by GC-MS, LC-MS and NMR.

6. Chemistry and Analysis

Chemical classification: azacyclics; azoles; benzimidazoles

Metodesnitazene is a 2-benzylbenzimidazole which is structurally related to the internationally controlled opioid etonitazene (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs). Metodesnitazene differs from etonitazene due to the absence of a nitro group at the 5-position of the benzimidazole moiety and the replacement of the ethoxy group present in etonitazene with a methoxy group.

Metodesnitazene is structurally similar to etazene, formally notified on 1 June 2020, differing only by replacement of the ethoxy group present in etazene, with a methoxy group. Metodesnitazene is the third substance from this group, the other two being etazene and isotonitazene, to have recently emerged on the drug market. Isotonitazene, which was formally notified in August 2019, has been the focus of an initial report [1], technical report [2] and has been subjected to an EMCDDA risk assessment on 26 May 2020.

The emergence of substances from within this group, was highlighted in section 2.2 'Notification in focus: Etazene' of the EU Early Warning System Situation Report, issued in June 2020. As mentioned in the Situation Report, we kindly request that the Network continue to report all identifications of these substances to the EMCDDA in order to help us understand the risks that these substances may pose to Europe.

While both etonitazene and isotonitazene are 5-nitro-2-benzylbenzimidazole derivatives, metodesnitazene, like etazene, lacks the nitro group at the 5-position of the benzyl moiety and, therefore, it is a 2-benzylbenzimidazole. The degree of analgesic activity in this series appears to be related to the substitution at the benzyl moiety (with para benzyl substituted derivatives displaying higher activity) and the position of the electron withdrawing nitro (-NO₂) group (with 5-nitro benzimidazole derivatives displaying higher activity) [3].

The synthesis of the hydrochloride salt was originally described by Hoffman *et al.* and Hunger *et al.* in the early 1960s [4-6]. A melting point of 150-151°C has been reported for the hydrochloride salt of metodesnitazene [4-6].

7. Pharmacology and toxicology

Pharmacological classification: opioid

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.

Metodesnitazene (compound XXVIII) [6] has been shown to have analgesic effects in mice, following subcutaneous administration in the tail-flick test metodesnitazene was assessed to have a potency equivalent to morphine [6,7].

Similar to other types of opioid analgesics such as morphine and fentanyl, the 2-benzylbenzimidazole compounds produce most of their effects by activating 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 will 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, the 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/1132>

9. Acknowledgements

The Belgian Early Warning System on Drugs is kindly acknowledged for the information and analytical data provided.

10. Attachments

None.

11. References

- [1] EMCDDA initial report on the new psychoactive substance *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (isotonitazene). 2020. https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en
- [2] EMCDDA technical report on the new psychoactive substance *N,N*-diethyl- 2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole- 1-ethanamine (isotonitazene). 2020. https://www.emcdda.europa.eu/publications/technical-reports/technical-report-isotonitazene_en
- [3] Hunger A, et al. Synthesis of analgesically active benzimidazole derivatives with basic substitutions. *Experientia*. 1957;13(10):400-1.
- [4] Hoffman K, et al. 1-(Tertiary aminoethyl)-2-(*p*-alkoxybenzyl)benzimidazoles. DE Patent. 1960; 1079646.
- [5] Hoffman K, et al. Basically substituted benzylbenzimidazoles. US Patent. 1961; 2980690
- [6] Hunger A, et al. Benzimidazol-Derivate und verwandte Heterocyclen. II. Synthese von 1-Aminoalkyl-2-benzyl-benzimidazolen. *Helvetica Chimica Acta*. 1960;43(3):800-9.
- [7] Casy AF, et al. Ionisation constants and partition coefficients of some analgesically active 2-benzylbenzimidazole derivatives and related compounds. *Journal of Pharmacy and Pharmacology*. 1966;18(10):677-83.