European Monitoring Centre for Drugs and Drug Addiction

EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	30 July 2020	RCS ID	EU-EWS-RCS-FN-2020-0026
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of ethyl 2-methylamino-1-phenylcyclohex-3-ene-1-carboxylate (nortilidine) by Poland 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 ethyl 2-methylamino-1-phenylcyclohex-3-ene-1-carboxylate (nortilidine) for the first time in Europe.

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

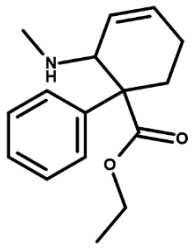
2. Data use restrictions

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: ethyl 2-methylamino-1-phenylcyclohex-3-ene-1-carboxylate
- Chemical names: ethyl 2-(methylamino)-1-phenyl-cyclohex-3-ene-1-carboxylate; ethyl 2-(methylamino)-1-phenylcyclohex-3-ene-1-carboxylate; ethyl 2-(methylamino)-1-phenyl-3-cyclohexene-1-carboxylate; 2-methylamino-1-phenyl-1-cyclohex-3-enecarboxylic acid ethyl ester; 2-methylamino-1-phenyl-cyclohex-3-ene-1-carboxylic acid ethyl ester
- Common name: nortilidine
- Other names: NRT; nortilidin; nortilidate
- Chemical formula: $C_{16}H_{21}NO_2$
- Molecular weight: 259.34
- CAS Registry number: 38677-94-0 (base); 34596-11-7 (hydrochloride salt)
- InChIKey: PDJZPNKVLDWEKI-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Opioid

5. Detection

Type: Seizure
Case Report identifier: EDND-CR-2020-329

Details: nortilidine was identified in 2 white round biconvex tablets seized by Police in Piotrków Trybunalski, on 26 May 2020. The tablets were contained in a plastic bag labelled with the name ‘Hyper’. The seizure is reported as a case of national trafficking, via a postal parcel.

The substance was analytically confirmed using GC-MS and LC-QTOF-MS/MS by the Central Forensic Laboratory of the Police.

6. Chemistry and Analysis

Chemical classification: other; unclassified

Nortilidine is the *N*-desmethyl derivative of the internationally controlled synthetic opioid tilidine (Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs). The difference between tilidine and nortilidine is the mono-demethylation of the tertiary amine in nortilidine [1].

Nortilidine was first described in a patent from the early 1970s investigating analgesic 3-(methylamino)-4-phenyl-4-(ethoxycarbonyl)cyclohexenes [2].

Nortilidine contains two chiral centres and therefore four possible enantiomers of the substance may exist. The enantiomers of nortilidine in human plasma have been determined using GC-MS [3].

The substances nortilidine and troparil, formally notified in 2018, are structural isomers. Nortilidine also shares some structural features with the opioid tramadol.

A reference standard is available for the hydrochloride salt of nortilidine [4,5].

7. Pharmacology and toxicology

Pharmacological classification: opioid

Nortilidine is reported to be the active metabolite of tilidine [6,7].

Tilidine is a synthetic opioid used for treatment of moderate or strong pain or for long-term treatment of patients with chronic pain and a World Health Organization class II analgesic [7]. The analgesic action of tilidine and nortilidine are reversed by naloxone [6]. Oral tilidine was found to be 1/8-1/10 as potent as parenteral morphine in producing morphine-like subjective effects [8]. Tilidine is available in a fixed combination with naloxone for oral administration, a mixture claimed to lower the abuse liability of tilidine [9]. It is commercialized under a number of product names, including Valoron N and Valtran. Cases of Valoron abuse and dependence have been reported in the literature [10,11]. Side effects of tilidine include hallucinations, euphoric mood, somnolence and confusion [12]. Tilidine is considered a prodrug, with its therapeutic activity derived from its metabolite nortilidine [6,7,13].

Nortilidine is reported to cross the blood-brain barrier easily, binding to the mu-opioid receptor as a potent agonist [7]. In a systematic study of the agonist and antagonist action of tilidine and nortilidine on recombinant human Delta opioid (DOP), Kappa opioid (KOP), Mu opioid (MOP), and nociception/orphanin (NOP) receptors, nortilidine was found to be a selective agonist of the MOP receptor displaying a potency about 100-fold higher than that of the parent molecule tilidine [6].

It is also reported that nortilidine is an NMDA receptor antagonist and dopamine reuptake inhibitor, equipotent to morphine [14].

Nortilidine is formed by demethylation of tilidine in the liver [7,13], with approximately two-thirds of the dose of tilidine metabolized to nortilidine in humans, although only one-third of the dose is available systemically as nortilidine, for interaction with the opiate receptors after both intravenous and oral dosing of tilidine [13]. Nortilidine is further demethylated to bisnortilidine, which has a low affinity for opiate receptors [7,13]. In a study investigating the sequential first-pass metabolism of nortilidine in humans, nortilidine could be readily detected in plasma a few minutes after intravenous administration of tilidine, with maximum plasma concentrations achieved after 0.5 hours [13]. When tilidine was administered orally, both tilidine and the metabolites nortilidine and bisnortilidine could be determined in plasma shortly after administration, with tmax values of 0.4, 0.7, and 1.2 hours, respectively [13]. Bisnortilidine appears to be one of the main metabolites of nortilidine, following intravenous administration of nortilidine [13].

8. Further information

Further information on this substance is available on the EDND profile:
https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1111

9. Acknowledgements

The Polish National Focal Point, Polish Police and the Central Forensic Laboratory of the Police are kindly acknowledged for the information and analytical data provided.

10. Attachments

None.

11. References

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