European Monitoring Centre
for Drugs and Drug Addiction

INITIAL REPORTS

ISSN 2600-0954

Isotonitazene

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)

In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended)

About this series

EMCDDA initial reports are drawn up on one or several similar new psychoactive substances that may pose health or social risks at European Union level.

Initial reports provide scientific evidence to the Commission in order to allow it to make an informed decision regarding whether or not there is a need to request a risk assessment on a new psychoactive substance.

Contents

Acknowledgements 3

Statement regarding the United Kingdom 4

1. Introduction 5

2. Information collection process 6

3. Information required by Article 5b(2) of the Regulation 8

3.1 Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance (Article 5b(2a)) 8

3.2 Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction (Article 5b2(b)) 10

3.3 Pharmacological and toxicological description of the new psychoactive substance (Article 5b2(c)) 13

3.4 Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance (Article 5b2(d)) 15

3.5 Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product 14

3.6 Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes 16

3.7 Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States 16

3.8 Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances 17

3.9 Other relevant information 17

4. Analysis and assessment 18

5. References 19

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein;
- the European Medicines Agency (EMA);
- the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Commission;
- the World Health Organization;
- Peter Blanckaert, Coordinator Belgian Early Warning System Drugs (BEWSD), Sciensano;
- István Ujváry, hon. associate professor, Budapest University of Technology and Economics; hon. associate professor, University of Szeged; iKem BT, Budapest.

Project team: Anabela Almeida, Rachel Christie, Michael Evans-Brown, Ana Gallegos, Rita Jorge, Joanna De Morais and Roumen Sedefov.

Project leaders: Michael Evans-Brown, Ana Gallegos and Roumen Sedefov**.**

Statement regarding the United Kingdom

The reference period for this report includes 2019 and 2020 (up to the moment of writing). The United Kingdom left the European Union as of 1 February 2020. However, during the transitional period, the UK continues to participate in the European Union Early Warning System on new psychoactive substances. Unless stated otherwise, for the purpose of this report, the term ‘Member States’ shall include the United Kingdom.

1. Introduction

N,*N*-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (isotonitazene) is a synthetic opioid analgesic. It is a member of the benzimidazole family of opioids which includes etonitazene, a potent internationally controlled opioid analgesic ([1]). Although the size of the market is unknown, isotonitazene is sold online as a legal replacement to controlled opioids; it also appears to have been sold on the illicit opioid market at street-level in a small number of countries. Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death.

In Europe, isotonitazene is monitored by the EMCDDA as a new psychoactive substance ([2]) through the European Union Early Warning System (EWS) in accordance with Article 5a of Regulation (EC) No 1920/2006 (as amended) ([3,4]).

Isotonitazene was formally notified as a new psychoactive substance ([5,6]) by the EMCDDA on behalf of Belgium on 26 August 2019. The notification was based on the identification of the substance in a collected sample of powder that was a test purchase from a private online vendor that was received on 1 July 2019. However, based on information subsequently reported to the EMCDDA concerning a seizure made by police in Estonia, isotonitazene has been available on the European drug market since at least April 2019.

Since the formal notification, information on isotonitazene has been exchanged between the EMCDDA and the European Union EWS Network (EMCDDA, Europol, Reitox national focal points, and the Commission); the EMA have been kept duly informed.

On 7 February 2020, the EMCDDA issued a public health advisory to the Network highlighting an increase in the number of identifications of isotonitazene in Europe and the potential risks posed by this. The advisory also informed the EWS Network that based on potential public health risks, the EMCDDA had added isotonitazene to the list of new psychoactive substances under intensive monitoring ([7]) and requested that the Network expedite reporting of any event involving isotonitazene to the EMCDDA until further notice.

([1]) Etonitazene is controlled under Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs. https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/58th_Edition/Yellow_List_-ENG.pdf

([2]) As defined in point 4 of Article 1 of Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking (OJ L 335, 11.11.2004, p. 8).

([3]) Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast) (O J L 376, 27.12.2006, p.1-13).

([4]) Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances (O J L 305, 21.11.2017, p.1-7).

([5]) EMCDDA (2020), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, p. 15–6. http://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

([6]) EMCDDA (2020), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 2. Formal notification of a new psychoactive substance. https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%202-%20Formal%20notification%20of%20a%20new%20psychoactive%20substance.pdf

([7]) EMCDDA (2020), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 6. Intensive monitoring.

Article 5b of Regulation (EC) No 1920/2006 (as amended) requires that '*Where the Centre, the Commission or a majority of the Member States considers that information shared on a new psychoactive substance collected pursuant to Article 5a in one or more Member States gives rise to concerns that the new psychoactive substance may pose health or social risks at Union level, the Centre shall draw up an initial report on the new psychoactive substance'*.

The initial report is submitted to the Commission and the Member States. The purpose of the initial report is to provide scientific evidence to the Commission to allow it to make an informed decision regarding whether or not there is a need to request a risk assessment on a new psychoactive substance as set out in Article 5c of Regulation (EC) No 1920/2006 (as amended).

Based on the information reported by the Network, on 20 February 2020, the EMCDDA assessed the existing information (8,9) on isotonitazene, based on the following criteria:

- reports of health problems;
- reports of social problems;
- reports of seized material;
- pharmacological and toxicological properties and analogy with better-studied substances; and,
- potential for further spread.

The EMCDDA concluded that the assessment gave rise to concerns that isotonitazene may pose health or social risks at Union level, and, consequently, determined that an initial report should be produced.

2. Information collection process

In accordance with the requirements of Article 5b of the Regulation, on 28 February 2020, the EMCDDA launched a procedure for the collection of additional information on isotonitazene in order to support the production of the initial report.

The EMCDDA collected information through:

- a structured reporting form to the Reitox national focal points in the Member States, Turkey, and Norway (Article 5b(4));
- routine monitoring of open source information;
- a search of open source information conducted specifically for the production of the initial report which included: scientific and medical literature, official reports, grey

http://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%206-%20Intensive%20monitoring.pdf

([8]) European Monitoring Centre for Drugs and Drug Addiction (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Publications Office of the European Union, Luxembourg. http://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

([9]) This included information reported to the EMCDDA through the Early Warning System, including case reports and aggregated datasets.

literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and online vendors.

In addition, the EMCDDA also submitted requests to:

- The World Health Organization (WHO) in order to determine if isotonitazene is under assessment or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances ('United Nations system').

- The European Medicines Agency (EMA) in order to determine if isotonitazene is used as an active substance in a medicinal product for human or veterinary use at Union or national level (Article 5b(5)). Specifically, the EMA was asked if isotonitazene is an active substance in:

  a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/EC of the European Parliament and of the Council ([10]), Directive 2001/82/EC of the European Parliament and of the Council ([11]) or Regulation (EC) No 726/2004 of the European Parliament and of the Council ([12]);

  b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

  c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;

  d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;

  e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council ([13]).

- Europol in order to provide information on the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of isotonitazene, and in any use of isotonitazene (Article 5b(6)).

- The European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) in

([10]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).
([11]) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).
([12]) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).
([13]) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

order to provide the information and data at their disposal on isotonitazene (Article 5b(7)).

The information collection process was concluded on 27 March 2020. The EMCDDA received responses from all 28 Member States, Turkey, and Norway. In addition, the EMCDDA received responses from WHO, EMA, Europol, ECHA, ECDC, and EFSA.

3. Information required by Article 5b(2) of the Regulation

The order and titles of subsections 3.1 to 3.9, below, are as they appear in Article 5b(2) of Regulation (EC) No 1920/2006 (as amended); sections 3.1 to 3.4 are cross-referenced with the headings of Article 5b(2a) to Article 5b(2d) of the Regulation.

3.1 Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance (Article 5b(2a))

As isotonitazene has only been on the drug market for a short period of time, it may not be part of drug screening in many forensic and toxicology laboratories. Therefore, the presence of isotonitazene on the European drug market may be undetected in some areas, including in law enforcement seizures as well as in biological samples related to serious adverse events. It is also important to note, that, due to differences in reporting practices across Europe, identifications of isotonitazene may be unreported to the Reitox national focal points and as a consequence to the EMCDDA.

3.1.1 Information from seizures, collected samples and biological samples

As of 28 March 2020, isotonitazene has been identified in six Member States: Belgium, Estonia, Germany, Latvia, Sweden, and the United Kingdom. These relate to police seizures reported by Estonia, Germany, and Latvia; a customs seizure reported by Sweden; a collected sample reported by Belgium; and biological samples from a death case reported by the United Kingdom.

Information from seizures

Law enforcement seizures of isotonitazene have been reported in four Member States: Estonia, Latvia, Germany, and Sweden. In total, 24 seizures were reported. In 22 cases isotonitazene was seized in powder form (total of 109.6 g of powder) and in two cases in liquid form (4.5 g).

Police seizures

A total of 23 seizures of isotonitazene made by police were reported by Estonia (n=17), Latvia (n=4), and Germany (n=2). Where known, the seizures took place between April 2019 and January 2020.

In 21 cases, isotonitazene was seized in powder form totalling 60.8 g (range from 0.013 to 19.8 g); the colour of the powder was described as brown in some of the cases reported by

Estonia. Information on the amount of isotonitazene present in the seizures was not reported. Estonia reported that the only other substances detected in the powders were ‘common sugars’ (not further specified); Latvia reported that one seizure also contained fentanyl. Estonia reported that some of the seizures related to small-scale distribution/supply. In one case reported by Latvia, powders of isotonitazene were found in 19 individual foil packages also suggesting small-scale distribution/supply.

In two cases reported by Germany, the seized products were liquids (product name: "ISOTONITAZEN EXTRA STRONG") and also contained trace amounts of the synthetic cannabinoid 5F-MDMB-P7AICA.

Customs seizures

Sweden reported one seizure of isotonitazene that was made by customs. The seizure took place in September 2019. A total of 48.8 g of powder was seized; the colour was described as yellow. Information on the amount of isotonitazene present in the seizure was not reported. The seized package originated from China and the destination was Sweden.

Information from collected samples

Belgium reported a collected sample of isotonitazene. It was a test purchase made by the national focal point via a private Telegram-group linked to a private website. The sample was incorrectly advertised as ‘etonitazene’. The cost was $400 per 1 g. It was received as a white powder in a plastic zip-lock bag which was then packaged inside a foil bag, with the label ‘iso’. Based on the analyses conducted, it was reported that the isotonitazene was supplied as its hydrochloride salt and that it was of ‘high purity’ (Blanckaert *et al*., 2019).

Information from biological samples

The United Kingdom reported biological samples (blood and urine) from a death in which isotonitazene was identified (Section 3.1.2).

3.1.2 Health problems

Germany reported a death involving isotonitazene; no further details are currently available.

The United Kingdom reported a death with confirmed exposure to isotonitazene; butyrylfentanyl, despropionyl fentanyl (4-ANPP), and despropionyl fluorofentanyl were also identified. All ‘were at very low (estimated sub ng/ml) levels)’. The death occurred in 2019; no further details are currently available.

As isotonitazene is an opioid analgesic, the health risks may have some similarities with those associated with controlled opioids such as heroin or the fentanils.

ECDC reported that currently they do not have any information on isotonitazene at their disposal, in particular any data on infectious diseases among isotonitazene users.

3.1.3 Social problems

There is no specific information on the social risks that may be associated with the use of

isotonitazene. As isotonitazene is an opioid analgesic, the social problems may have some similarities with those associated with controlled opioids such as heroin or the fentanils.

3.1.4 Patterns of use

There is limited information on the patterns of use of isotonitazene. As isotonitazene is an opioid analgesic, it could be expected that suppliers as well as users who are looking for substitutes for controlled opioids, such as heroin, fentanils, and/or prescription opioids, may be interested in isotonitazene.

User groups may include high-risk drug users, including individuals who inject opioids. Similar to other new psychoactive substances, it also appears that there is interest in isotonitazene by some psychonauts.

Anecdotal reports from user websites note a range of routes of administration and doses, including use by intravenous injection and nasal sprays ([14,15]).

Isotonitazene may be deliberately sought after by some users; others, such as those that purchase it at street-level, may be unaware that they are using the substance which presents an inherent risk to the individuals.

3.2 Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction (Article 5b2(b))

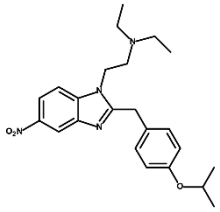
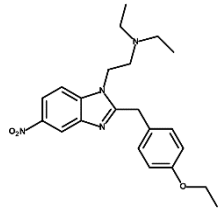
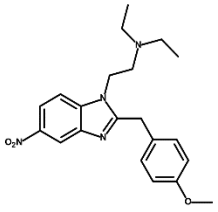
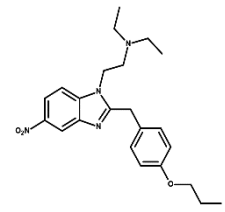
3.2.1 Chemical description and names

Isotonitazene belongs to the benzimidazole group of synthetic opioids. In particular, it is a 6-nitro-2-benzylbenzimidazole. This group also includes etonitazene, which is internationally controlled, as well as metonitazene, and protonitazene ([16]).

Isotonitazene differs from these substances in the substitution at the *para*-position of the benzyl moiety, which is an iso-propoxy group in isotonitazene, an ethoxy group in etonitazene, a methoxy group in metonitazene, and a propoxy group in protonitazene. The molecular structure, molecular formula and molecular mass of isotonitazene are provided in the figure.

([14]) https://www.google.com/search?q=site%3A.bluelight.org+isotonitazene&ie=utf-8&oe=utf-8
([15]) https://www.google.com/search?q=site%3A.reddit.com+isotonitazene&ie=utf-8&oe=utf-8
([16]) As of March 2020, neither the identification of metonitazene nor protonitazene have been reported to the EMCDDA via the Early Warning System.

FIGURE
Molecular structure, molecular formula, and molecular mass of isotonitazene. Information on etonitazene, metonitazene, and protonitazene is provided for comparison.

				
	isotonitazene	etonitazene ([17])	metonitazene ([18])	protonitazene ([19])
Molecular formula	$C_{23}H_{30}N_4O_3$	$C_{22}H_{28}N_4O_3$	$C_{21}H_{26}N_4O_3$	$C_{23}H_{30}N_4O_3$
Molecular mass	410.52	396.48	382.46	410.52

Common name:

Isotonitazene

Systematic (IUPAC) name:

N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine

Other chemical names:

N,N-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine

N,N-diethyl-2-[2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl]ethanamine

N,N-diethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine

N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine

N,N-diethyl-2-[5-nitro-[2-[(4-propan-2-yloxyphenyl)methyl]benzimidazol-1-yl]-ethanamine

1-[2-(diethylamino)ethyl]-2-(*p*-isopropoxybenzyl)-5-nitrobenzimidazole

([17]) *N,N*-diethyl-2-[(4-ethoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine
([18]) *N,N*-diethyl-2-[(4-methoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine
([19]) *N,N*-diethyl-2-[(4-propoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine

Street names:

'iso'

Chemical Abstracts Service (CAS) registry numbers:

14188-81-9 free base

119276-00-5 hydrochloride salt

IUPAC International Chemical Identifier Key (InCHI Key):

OIOQREYBGDAYGT-UHFFFAOYSA-N

Simplified Molecular-Input Line-Entry System (SMILES):

CCN(CC)CCN1C(CC2=CC=C(OC(C)C)C=C2)=NC3=CC([N+]([O-])=O)=CC=C31

3.2.2 Physical description

Both the free base and salts of isotonitazene are solids.

The measured melting point for isotonitazene hydrochloride salt is 172–173 °C (Hoffmann *et al*., 1960; Hunger *et al*., 1960) ([20]).

Isotonitazene is lipophilic ([21]).

Isotonitazene, as both the freebase and the hydrochloride salt, is soluble in methanol (NPS Discovery, 2019; Blanckaert *et al*., 2019) and in dimethyl sulfoxide (DMSO) (Blanckaert *et al*., 2019).

To date, seizures and collected samples containing isotonitazene reported to the EMCDDA have been in brown, yellow and white powders. In addition, isotonitazene has also been identified in liquid form. Identifications of isotonitazene reported to the EMCDDA include both the hydrochloride salt and the free base of the substance.

3.2.3 Methods and chemical precursors used for the manufacture or extraction

No information was reported by the Member States, Norway, or Turkey about the chemical precursors or manufacturing methods used to make the isotonitazene which has been identified within Europe.

The synthesis of isotonitazene is reported in Hoffmann *et al*., (1960). It involves the condensation of the *ortho*-phenylenediamine derivative, obtained from 1-chloro-2,4-dinitrobenzene, in two steps, with phenylacetic acid, benzylcyanide or the corresponding imidate.

([20]) Belgium reported a collected sample of isotonitazene, purchased through a private Telegram-group. Analysis confirmed the hydrochloride salt of isotonitazene. Melting point analysis was conducted and the obtained result of 174 °C is in accordance with reported literature values.
([21]) The calculated octanol/water distribution coefficient for isotonitazene is logP = 4.85, using *Molinspiration property engine v2018.10* (https://www.molinspiration.com/cgi-bin/properties).

Although there is no information on the actual manufacturing methods used to make the isotonitazene which has been identified in Europe, one possible synthetic route is an improved method described for the synthesis of etonitazene by Carroll *et al*., (1975). The authors describe the method as simple, producing high yields, which can be adapted to both large scale preparations and for the preparations of other benzimidazole opioids (Carroll *et al*., 1975). Additionally, alkylation by isopropyl bromide of a phenolic species ('desethyletonitazene'), which was reported to be a versatile precursor for other homologues (Hoffmann *et al*., 1959; Hoffmann *et al*., 1960), may also be used to produce isotonitazene.

Analytically confirmed detections of the related substance etonitazene on the illicit drug market in Moscow, Russia, were reported in 1998 and 1999 (Sorokin *et al*., 1999a; Sorokin *et al*., 1999b). Information from one of these cases noted that the substance had been synthesised in Russia, using a modification of a method published by Hunger *et al.* (1960). These reports also noted the identification of etonitazene on the illicit drug market in Germany in 1987, which also apparently used the synthetic route described by Hunger *et al*., (1960).

Recently, a 'one-pot', three component synthesis producing benzimidazole opioids at high yield has also been reported (Kim *et al*., 2011).

3.2.4 Detection and analysis

Methods documented in the literature for the identification of isotonitazene in physical samples include: gas chromatography–mass spectrometry (GC-MS) (NPS Discovery, 2019; Blanckaert *et al*., 2019; Cayman Chemical, 2020); Fourier transform infrared spectroscopy (FTIR), ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), Raman spectroscopy and ultraviolet spectroscopy (Blanckaert *et al*., 2019); and high-performance liquid chromatography (HPLC) (Blanckaert *et al*., 2019; Krotulski *et al*., 2020).

Methods have also been documented in the literature for the identification of isotonitazene in biological samples, which include HPLC and liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Krotulski *et al*., 2020).

In the analysis by Blanckaert *et al*., isotonitazene was the only substance present in the sample and no impurities were identified (Blanckaert *et al*., 2019). The authors concluded that the sample was of high purity (Blanckaert *et al*., 2019).

In the analysis of biological samples by Krotulski *et al*., the need for increased analytical sensitivity when testing for isotonitazene was highlighted following quantitative results which were in the low sub-nanogram per millilitre range (Krotulski *et al*., 2020).

It is important to note that, since isotonitazene and protonitazene have the same molecular mass, their GC-MS analysis will result in very similar mass spectrometry fragmentation patterns. The ability to distinguish between isomers requires the use of analytical reference

standards, access to reference spectra for both substances, or additional analytical methods ([22]).

Isotonitazene is available as analytical reference material ([23]).

3.3 Pharmacological and toxicological description of the new psychoactive substance (Article 5b2(c))

Isotonitazene is a synthetic opioid analgesic. It is a member of the benzimidazole family of opioids which includes etonitazene, a potent internationally controlled opioid analgesic.

The available information suggests that isotonitazene may be a potent opioid in humans (Hunger *et al*, 1960; Blanckaert *et al*., 2019). As such, the effects of isotonitazene are likely to share similarities with etonitazene, as well as fentanyl and other opioid analgesics.

The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential (Herz, 1993; Kieffer, 1999; Pasternak and Pan, 2013; Pattinson, 2008; Romberg *et al*., 2003).

Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death (EMCDDA, 2017; Pattinson, 2008; White and Irvine, 1999). This risk may be greater due to the fact that isotonitazene is the first of the benzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this family of opioids, including a lack of information on what doses to use and what effects the substance can have. The timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics (Kim and Nelson, 2015; Boyer, 2012).

Similarly to other opioid analgesics, the use of isotonitazene with other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics, alcohol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, is likely to produce additive depressant effects which can increase the risk of life-threatening respiratory depression and arrest.

While there is limited information for isotonitazene, the chronic health risks might share some similarities to those seen with established opioids, such as heroin and other fentanils. This may include dependence.

ECHA reported to the EMCDDA that they do not currently have any information on isotonitazene at their disposal, in particular any data on its toxicological properties. EFSA reported to the EMCDDA that they do not currently have any information on isotonitazene at their disposal with regards to its acute or chronic toxicity.

([22]) Reference standard material for protonitazene is available: https://www.caymanchem.com/product/29381
([23]) https://www.caymanchem.com/product/27255

3.4 Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance (Article 5b2(d))

Europol received replies from 13 Member States: Bulgaria, Croatia, Denmark, Finland, Greece, Hungary, Ireland, Lithuania, Luxembourg, Poland, Slovakia, Sweden, and the United Kingdom.

Replies were also received from Norway and the United States Drug Enforcement Administration (DEA) ([24]).

No information was received on the involvement of criminal groups in the manufacture or distribution of isotonitazene. In addition, no information was received in relation to the production, distribution (seizures), or trafficking of isotonitazene.

The United Kingdom reported that isotonitazene can be purchased on the internet. They also reported that there is no information available on the involvement of organised crime in the manufacture or distribution of isotonitazene in the United Kingdom.

Europol reported two cases linked to the structurally related substances etonitazene and metonitazene. One case involves several ongoing investigations in Czechia regarding the purchase of drugs on the darknet. The second case, from 2018 and still under investigation, involves seizures of postal parcels in Finland mailed predominately from Poland and which mostly related to 2-furanylfentanyl. As part of this investigation, Finland noted that the substance metonitazene appeared to be available online in 2018.

3.5 Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product

Based on the reported information from the EMA ([25]), it appears that isotonitazene is not an active substance in:

a. a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/ EC of the European Parliament and of the Council, Directive 2001/82/EC of the European Parliament and of the Council or Regulation (EC) No 726/2004 of the European Parliament and of the Council;

b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

([24]) The formal identification of isotonitazene by the U.S. DEA has not yet been reported. Isotonitazene is not a controlled substance or listed chemical under the U.S. Controlled Substances Act. If intended for human consumption, it may be treated as a controlled substance analogue, as defined in 21 U.S.C. 802(32)(A), as of October 27, 1986. Reporting indicates that the Canadian Border Services Agency (CBSA) has issued alerts on isotonitazene from seizures. Samples of isotonitazene have been reported by the US Customs and Borders Protection (CBP).
([25]) 27 Member States, as well as Norway and Iceland provided a response to the EMA's request regarding human and/or veterinary medicinal products. The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority.

In addition, it appears that isotonitazene is not an active substance in the following, although the information, especially in relation to use in extemporaneously prepared products, is unknown in some cases:

d. an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/ EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;

e. an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council.

3.6 Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes

Isotonitazene is used as an analytical reference material in clinical and forensic case work as well as scientific research. There is currently no information that suggests isotonitazene is used for other legitimate purposes.

ECHA and EFSA reported that isotonitazene did not retrieve any results in their databases.

3.7 Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States

Twenty-two Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) reported that isotonitazene is not subject to restrictive measures at national level. Turkey also reported that isotonitazene is not subject to restrictive measures at national level.

Drug control legislation

Four Member States (Estonia, Latvia, Poland, and Sweden) reported that isotonitazene is controlled under drug control legislation.

- Estonia reported that isotonitazene is controlled under the Act on Narcotic Drugs and Psychotropic Substances and Precursors thereof, Annex 1. Narcotic Drugs and Psychotropic Substances list since 17 January 2020.
- Latvia reported that isotonitazene is controlled under drug control legislation as a structural analogue of etonitazene.
- Poland reported that isotonitazene is controlled according to the general definition of the ‘substitute drug’.
- Sweden reported that isotonitazene is regulated as a narcotic since 11 February 2020.

New psychoactive substance legislation

The United Kingdom reported that isotonitazene is controlled under the Psychoactive Substances Act 2016.

Medicines legislation

Lithuania and Norway reported that isotonitazene is controlled under medicines legislation.

- Lithuania reported that isotonitazene is controlled under medicines legislation since 11 December 2019.
- Norway reported that isotonitazene is controlled under the Norwegian Medicines Act.

3.8 Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific, and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

On 22 March 2020, the World Health Organization informed the EMCDDA that isotonitazene is not currently under assessment nor has it been under assessment by the United Nations system.

3.9 Other relevant information

Information from other countries

Isotonitazene has been identified in 3 deaths in Canada. The deaths occurred in Alberta in March, September, and October 2019 (Toxicovigilance Canada, 2019). In addition, isotonitazene has been identified in falsified opioid analgesic medicines sold as Dilaudid tablets (hydromorphone hydrochloride) that were seized by police during February 2020 (Halifax Police, 2020).

Isotonitazene has been identified in at least 18 deaths in the United States. The deaths occurred between August 2019 and January 2020 and were from the Midwestern United States. Based on information from the death investigations and forensic toxicology results, at least some of the individuals were high-risk drug users and included people who had a history of injecting opioids such as heroin. Isotonitazene was identified along with one or more other psychoactive substances (controlled drugs and new psychoactive substances) in all the deaths, which suggests that polydrug use was common in these individuals. In particular, many of the cases involved the use of other CNS depressants along with isotonitazene (such as other opioids and/or benzodiazepines) (Krotulski *et al*., 2020).

4. Analysis and assessment

N,*N*-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (isotonitazene) is a synthetic opioid analgesic. It is monitored by the EMCDDA as a new psychoactive substance in accordance with Regulation (EC) No 1920/2006 (as amended).

Isotonitazene is a member of the benzimidazole family of opioids which includes etonitazene, a potent internationally controlled opioid analgesic. Currently available information suggests that isotonitazene may be a highly potent opioid analgesic. As such, the most serious acute risk from the use of isotonitazene is likely to be from respiratory depression, which can lead to apnoea, respiratory arrest, and death. Isotonitazene is the first of the benzimidazole opioids to be identified on the drug market in recent years, and users have no experience with this group of opioids (such as dose and effects) which may increase the risk of accidental life-threatening poisoning. This risk will be especially high if users are unaware that they are using isotonitazene, which may be the case when it is sold at street-level on the illicit opioid market. Importantly, the timely administration of the antidote naloxone has been shown to be effective in reversing respiratory depression caused by potent opioid analgesics such as isotonitazene.

Isotonitazene has been available on the drug market in Europe since at least April 2019. The most recent identification of isotonitazene reported to the EMCDDA is a seizure made by police in January 2020. As of 28 March 2020, it has been identified in six Member States: Belgium, Estonia, Germany, Latvia, Sweden, and the United Kingdom. These detections relate to police seizures reported by Estonia, Germany, and Latvia; a customs seizure reported by Sweden; a collected sample reported by Belgium; and biological samples from a death case reported by the United Kingdom. While the detected quantities are relatively small, they should be seen within the context of the possible high potency of isotonitazene.

It is important to note that the presence of isotonitazene on the drug market and in serious adverse events may be undetected in Europe since the substance is not routinely screened for in some laboratories. In addition, analytical sensitivity related to the analysis of biological samples from serious adverse events is a possible issue as the concentration of isotonitazene can be sub-nanogram to picogram.

A total of two deaths involving isotonitazene have been reported by Germany and the United Kingdom. In addition, deaths have been reported in Canada (3 cases) and the United States (18 cases). At least some of the individuals from the United States were high-risk drug users and included people who had a history of injecting opioids such as heroin; polydrug use, especially use of two or more CNS depressants, was common.

There is limited information on the manufacture, trafficking, distribution, and use of isotonitazene. It appears that at least some of the isotonitazene on the market in Europe has been produced by chemical companies based in China. It is sold online as a powder in small and wholesale amounts; it is also sold as ready to-use nasal sprays. Isotonitazene may also have also been sold on the illicit opioid market at street-level in at least two Member States. Isotonitazene may be deliberately sought after by some users; others, such as those that purchase it at street-level, may be unaware that they are using the substance which presents an inherent risk to the individuals. There is no information whether or not criminal groups are involved in the manufacture, trafficking, and distribution of isotonitazene within

Europe. The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution, and use of isotonitazene is currently unknown. It is conceivable, that, should there be a reduced availability of established opioids in Europe, such as heroin, then criminal groups, as well as people who use opioids (especially high-risk opioid users), may use a range of replacement substances, including benzimidazole opioids such as isotonitazene.

Isotonitazene has not been subject to assessment nor is currently under assessment by the United Nations system. Based on the available information, it appears that isotonitazene is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe. However, the use of isotonitazene as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States.

There is currently no information that suggests isotonitazene is used for other legitimate purposes.

Isotonitazene is subject to restrictive measures in six Member States: in Estonia, Latvia, Poland, and Sweden the substance is controlled under drug control legislation; in Lithuania it is controlled under medicines legislation; while in the United Kingdom it is controlled by new psychoactive substance legislation. In addition, isotonitazene is controlled under medicines legislation in Norway. It is unknown if isotonitazene is controlled in China, where at least some of the substance on the European market has been sourced from.

The EMCDDA will continue to intensively monitor isotonitazene in order to ensure that new information is provided to the Member States, Europol, the Commission, and the EMA via the European Union Early Warning System in a timely manner in order to strengthen situational awareness as well as inform preparedness and response measures at both national and EU level in order to protect public health.

Based on the analysis of the available information, the EMCDDA considers that there are indications that isotonitazene may pose health or social risks at Union level. We conclude that the potential health and social risks posed by the use, manufacture, distribution and the involvement of criminal groups, could be thoroughly assessed through a risk assessment procedure in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended).

5. References

Blanckaert, P. Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S. and Stove C. (2019), 'Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene', *Drug Testing and Analysis*. https://doi.org/10.1002/dta.2738

Boyer, E.W., (2012), 'Management of opioid analgesic overdose', *New England Journal of Medicine,* 367(2), pp. 146–155. https://doi.org/10.1056/NEJMra1202561

Carroll, F. I., and Coleman, M. C. (1975), 'Etonitazene. An improved synthesis', *Journal of Medicinal Chemistry,* 18(3), pp. 318–320.

Cayman Chemical (2020), 'Product Information: Isotonitazene', https://www.caymanchem.com/product/27255

EMCDDA (2017), Risk assessment report on a new psychoactive substance: *N*-phenyl-*N*-(1-(2-phenylethyl)piperidin-4-yl)furan-2-carboxamide (furanylfentanyl), Publications Office of the European Union, Luxembourg. https://doi.org/10.2810/716236

Halifax Police (2020), Police warn public of potent synthetic opioid found in Halifax. https://www.halifax.ca/home/news/police-warn-public-potent-synthetic-opioid-found-halifax

Herz, A. (ed)., (1993). Opioids II. Springer-Verlag, Berlin.

Hoffmann, K., Hunger, A., Kebrle, J., and Rossi, A. (1959), 'Verfahren für Herstellung analgetisch wirksamer Benzimidazole', Bundesrepublik Deutschland Patent No. DBP 1057123.

Hoffmann, K., Hunger, A., Kebrle, J., and Rossi, A. (1960), 'Benzimidazoles', US Patent No. 2935514.

Hunger, A., Kebrle, J., Rossi, A., and Hoffmann, K. (1960), 'Benzimidazole-Derivate und verwandte Heterocyclen III. Synthese von 1-Aminoalkyl-2-benzyl-nitro-benzimidazolen', *Helvetica Chimica Acta,* 43(4), pp. 1032–1046.

Kieffer, B. L., (1999), 'Opioids: first lessons from knockout mice', *Trends in Pharmacological Sciences*, 20, pp. 19–26. https://doi.org/10.1016/S0165-6147(98)01279-6

Kim, H. K. and Nelson, L. S., (2015), 'Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review', *Expert Opinion on Drug Safety*, 14(7), 1137–1146. https://doi.org/10.1517/14740338.2015.1037274

Kim, Y., Kumar, M. R., Park, N., Heo, Y., and Lee, S. (2011), 'Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and C–N bond formation', *The Journal of Organic Chemistry*, 76(23), pp. 9577–9583.

Krotulski, A., Papsun, D.M., Kacinko, S.L. and Logan, B.K., (2020), 'Isotonitazene quantitation and metabolite discovery in authentic forensic casework', *Journal of Analytical Toxicology*. https://doi.org/10.1093/jat/bkaa016

NPS Discovery (2019), 'Isotonitazene', Center for Forensic Science Research and Education (CFSRE). https://www.npsdiscovery.org/wp-content/uploads/2019/11/Isotonitazene_112119_ToxicologyAnalyticalReport.pdf.

Pasternak, G. W. and Pan, Y. X., (2013), 'Mu opioids and their receptors: evolution of a concept', *Pharmacological Reviews*, 65(4), pp. 1257–1317. https://doi.org/10.1124/pr.112.007138

Pattinson, K. T., (2008), 'Opioids and the control of respiration', *British Journal of Anaesthesia*, 100(6), pp. 747–758. https://doi.org/10.1093/bja/aen094

Romberg, R., Sarton, E., Teppema, L., Matthes, H. W. D., Kieffer, B. L. and Dahan, A., (2003), 'Comparison of morphine-6-glucuronide and morphine on respiratory depressant and antinociceptive responses in wild type and μ-opioid receptor deficient mice', *British Journal of Anaesthesia*, 91, pp. 862–870. https://doi.org/10.1093/bja/aeg279

Sorokin, V. I., Ponkratov, K. V., and Drozdov, M. A., (1999a), 'Etonitazene encountered in Moscow'. *Microgram*, XXXII(9), pp. 239–44.

Sorokin, V. I., (1999b), 'Illegal synthesis of etonitazene'. *Journal of the Clandestine Laboratory Investigating Chemists Association*, 9(2–3), pp. 20.

Toxicovigilance Canada (2019), *Isotonitazene: Newly identified opioid in Alberta*, 11 October 2019.

White, J. M. and Irvine, R. J., (1999), 'Mechanisms of fatal opioid overdose', Addiction, 94, pp. 961–972. https://doi.org/10.1046/j.1360-0443.1999.9479612.x

TD-AZ-20-001-EN-N

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2020), *EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene)*, Initial reports, Publications Office of the European Union, Luxembourg.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

More information

More information about the work and main outputs of the EU Early Warning System on new psychoactive substances:

| Early Warning System on NPS: www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en

Luxembourg: Publications Office of the European Union

doi:10.2810/370922 | ISBN 978-92-9497-491-4 | ISSN 2600-0954

EMCDDA, Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 | info@emcdda.europa.eu
emcdda.europa.eu | twitter.com/emcdda | facebook.com/emcdda