EUDA
EUROPEAN UNION DRUGS AGENCY

INITIAL REPORTS

Cychlorphine

EUDA initial report on the new psychoactive substance: 3-(3-{1-[1-(4-chlorophenyl)ethyl]piperidin-4-yl}-2-oxo-2,3-dihydro-1*H*-1,3-benzimidazol-1-yl)propanenitrile (cychlorphine)

In accordance with Article 9 of Regulation (EU) 2023/1322

Contents

Acknowledgements

The European Union Drugs Agency (EUDA) acknowledges the essential role of the Reitox national focal points and their national early warning systems in the Member States for collecting and reporting national data and sharing expertise. We also thank the following partners for their contributions: Europol and its National Units, the European Medicines Agency (EMA) and national competent authorities, the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the World Health Organization.

1. Introduction

3-(3-{1-[1-(4-Chlorophenyl)ethyl]piperidin-4-yl}-2-oxo-2,3-dihydro-1*H*-1,3-benzimidazol-1-yl)propanenitrile, commonly known as cychlorphine, is a piperidine benzimidazolone and synthetic opioid belonging to the orphine opioids, a group of related new synthetic opioids. Cychlorphine is structurally related to brorphine and bezitramide, both of which are controlled under Schedule I of the United Nations 1961 Single Convention on Narcotic Drugs because of the public health and social risks they pose.

Cychlorphine is monitored by the EUDA as a new psychoactive substance through the European Union Early Warning System (EWS), in accordance with Regulation (EU) 2023/1322 ([1]).

Since 2024, a marked increase has been observed in the number of orphine opioids identified on the European drug market, with nine new substances reported, including cychlorphine.

Cychlorphine was formally notified as a new psychoactive substance by the EUDA on behalf of Sweden on 24 February 2025 ([2,3]). The notification was based on the identification of the substance in 0.96 grams of white-beige powder that was seized by police on 14 August 2024. The substance was analytically confirmed using GC-MS and NMR.

On 14 March 2025, the EUDA placed cychlorphine under intensive monitoring due to concerns about potential public health risks. This requires the Member States to expedite reporting of any events involving the substance to the EUDA.

On 10 March 2026, the EUDA issued an advisory to the Member States on the increased availability of orphine opioids and associated harms in the European Union (EU). It noted that reports from the EU indicate an increase in availability and harms from 2025 onwards, particularly involving cychlorphine and, to a lesser degree, spirochlorphine. This trend was also consistent with reports from the United Kingdom, the United States, and Canada. The increase may be linked in part to the generic control of nitazene opioids in China in July

([1]) Regulation (EU) 2023/1322 of the European Parliament and of the Council of 27 June 2023 on the European Union Drugs Agency (EUDA) and repealing Regulation (EC) No 1920/2006. https://eur-lex.europa.eu/eli/reg/2023/1322/oj/eng
([2]) EMCDDA (2020), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, p. 15–6. http://www.euda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en
([3]) 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.euda.europa.eu/system/files/media/publications/documents/12213/Guidance%20Note%202-%20Formal%20notification%20of%20a%20new%20psychoactive%20substance.pdf

2025, a measure that may have contributed to reduced nitazene availability and the emergence of orphine opioids as substitute substances.

Article 9(1) of Regulation (EU) 2023/1322 requires that 'Where the Agency, the Commission or a majority of Member States considers that information on a new psychoactive substance collected in one or more Member States and shared with it or them gives rise to concerns that the new psychoactive substance might pose health or social risks at Union level, the Agency shall draw up an initial report on the new psychoactive substance.'

The initial report is submitted to the Commission to provide it with the evidence needed to decide whether to request a risk assessment on a new psychoactive substance under Article 10 of the Regulation.

On 13 April 2026, based on information reported by the Member States through the EWS, the EUDA assessed the available information on cychlorphine against the following criteria:

1. reports of health problems;
2. reports of social problems;
3. reports of seized material;
4. pharmacological and toxicological properties and analogy with better-studied substances; and
5. potential for further spread.

Based on its assessment, the EUDA determined that the available information on cychlorphine met criteria 1, 3, 4, and 5. The EUDA concluded that cychlorphine may pose health or social risks at Union level and consequently determined that an initial report should be produced.

In parallel, the EUDA also assessed the available information on the related orphine opioid spirochlorphine and determined that an initial report should also be prepared (EUDA, 2026a).

2. Information collection process

In accordance with Article 9 of Regulation (EU) 2023/1322, on 15 April 2026 the EUDA launched a procedure to collect further information on cychlorphine in order to prepare this initial report.

The EUDA collected information through:

- A data collection exercise distributed to the Reitox national focal points in the Member States, Türkiye, and Norway (Article 9(4));
- An open-source search covering scientific and medical literature, official reports, grey literature, drug discussion forums and related websites (hereafter 'user websites'), and online vendors.

In addition, the EUDA also submitted requests to:

- The World Health Organization (WHO) to determine if cychlorphine 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) to determine if cychlorphine is used as an active substance in a medicinal product for human or veterinary use at Union or national level (Article 9(5)). Specifically, the EMA was asked if cychlorphine is an active substance in:
    - 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 ([4]), Regulation (EC) No 726/2004 ([5]) or Regulation (EU) 2019/6 of the European Parliament and of the Council ([6]);
    - a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;
    - a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;
    - 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 in accordance with Article 112(1), point (c), of Regulation (EU) 2019/6;

([4]) 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). https://eur-lex.europa.eu/eli/dir/2001/83
([5]) 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).
([6]) 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).

  - 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 ([7]).

- Europol, to provide information on the involvement of criminal groups in the manufacture, distribution and distribution methods and trafficking of cychlorphine, and on any use of the new psychoactive substance (Article 9(6)).

- the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA), to provide information and data at their disposal on cychlorphine (Article 9(7)).

The information collection process was largely concluded on 18 May 2026. The EUDA received responses from the 27 Member States, Türkiye, and Norway. In addition, the EUDA received responses from EMA, Europol, ECHA, ECDC, EFSA and WHO.

3. Methodological note

The following complementary data sources have been used in the preparation of this initial report. Further details on the definitions and terminology used are provided in the EWS operating guidelines ([8]).

Routine data: For the period from 1 January 2024 to 31 December 2025, the report draws on annual aggregated data submitted to the EUDA. The 2025 data remain preliminary and may be subject to revision. Event-based data reported through the European Database on New Drugs (EDND) were also used.

Data collected for this report: Data reported by the Reitox national focal points in the Member States for the purposes of this initial report, as well as responses to ad hoc information requests, were also used.

Open-source information: Open-source information identified through routine monitoring was also used and, where the source or content required confirmation, verified with the Reitox national focal points.

([7]) 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. https://eur-lex.europa.eu/eli/dir/2001/20
([8]) EMCDDA (2020), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances. http://www.euda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

4. Information required by Article 9(2) of the Regulation

Subsections 4.1 to 4.9 follow the structure of Article 9(2) of Regulation (EU) 2023/1322, with corresponding provisions noted in each heading.

4.1 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 9(2a))

4.1.1 Information from seizures, collected samples and biological samples

First identification in Europe

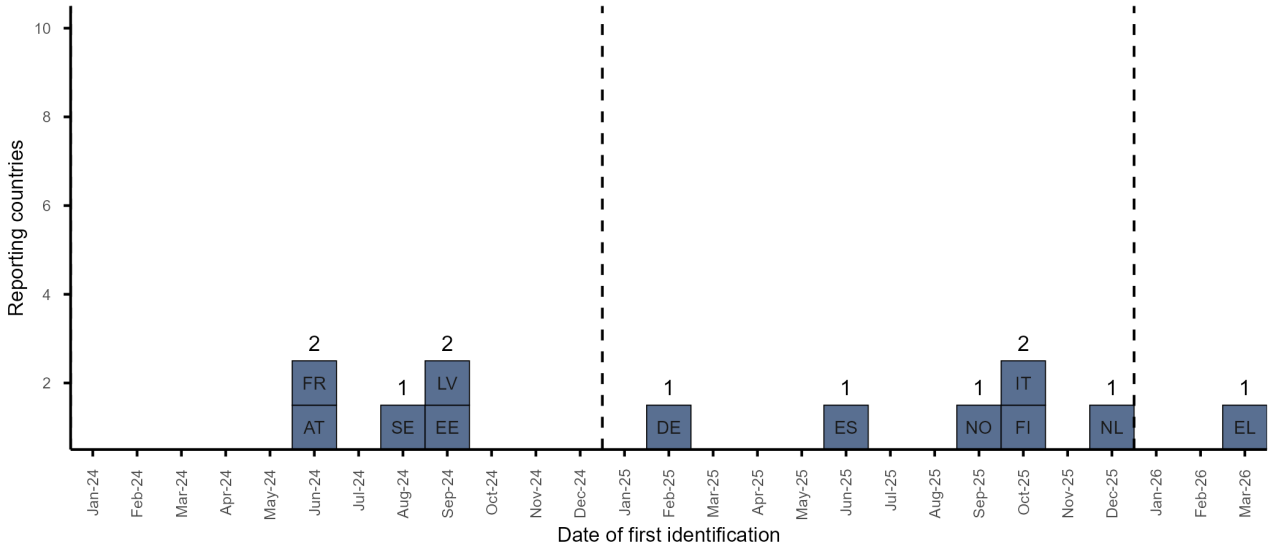
The first identification of cychlorphine in Europe was reported by Sweden based on its identification in a seizure made by police on 14 August 2024. Cychlorphine was identified in 0.96 grams of white-beige powder. The substance was analytically confirmed using GC-MS and NMR.

However, subsequent information reported to EUDA, relating to cases submitted by Austria and France, indicates that cychlorphine may have been present on the European drug market as early as June 2024.

First identifications in country

Eleven Member States reported the first identification of cychlorphine in their territory between June 2024 and March 2026: Austria, Estonia, Finland, France, Greece, Germany, Italy, Latvia, The Netherlands, Spain, and Sweden. Norway also reported its first identification during this period (Figure 1).

Figure 1. Countries reporting the first identification of cychlorphine in their territory, by month of identification, 2024–2026



Note: EU two-letter country codes are used to identify each country.

Information from seizures

Eight Member States and Norway reported a total of 228 seizures of cychlorphine between June 2024 and March 2026: Austria (n=1), Estonia (n=108), Finland (n=3), Germany (n=1), Latvia (n=107), the Netherlands (n=2), Spain (n=1), Sweden (n=4), and Norway (n=1) (Figure 2) ([9]).

The number of cychlorphine seizures rose from 18 cases in 2024 to 142 cases in 2025. So far in 2026 (through March), a further 68 seizures have been reported.

During the 2024–2026 period, 210 cases of seizures of material containing cychlorphine were reported, amounting to a total of 6.46 kg of material: 0.08 kg in 15 cases in 2024, 5.78 kg in 128 cases in 2025, and 0.60 kg in 67 cases in 2026 (through March).

The majority was seized by Estonia (4.57 kg; 71%), followed by Latvia (1.88 kg; 29%). Powders accounted for 134 cases (64%); the remaining 76 cases (36%) comprised 3 liquid cases and 73 cases involving other or unspecified forms.

([9]) Norway reported three additional customs seizures totalling 3 g of material and 50 blotters seized between September 2025 and March 2026. All cases were reported as originating from Greece, and in all three cases, cychlorphine was seized alongside other substances. As these cases were not analytically confirmed, they were not included in the analysis.

When reported, powders were described as beige or white-beige. The purity of the powders was not reported. In one case reported by Sweden, a package of beige powder was labelled as ‘C’.

Between 2024 and 2026, a total of 4,013 mL of cychlorphine was seized in 12 cases. In 2024, 10.22 mL of material seized were reported in three cases; in 2025, 4,001 mL were reported in eight cases; in 2026 (through March), 1.3 mL was reported in one case. More than 99% of the entire quantity seized originated from a single seizure reported by Germany in 2025 (4,001 mL; 99.7%). In the case reported by Germany, the seized product was a colourless e-liquid in a propylene glycol matrix with a reported cychlorphine concentration of approximately 0.5-1 mg/mL. In one case reported by Sweden, the liquid sample was contained in a nasal spray bottle.

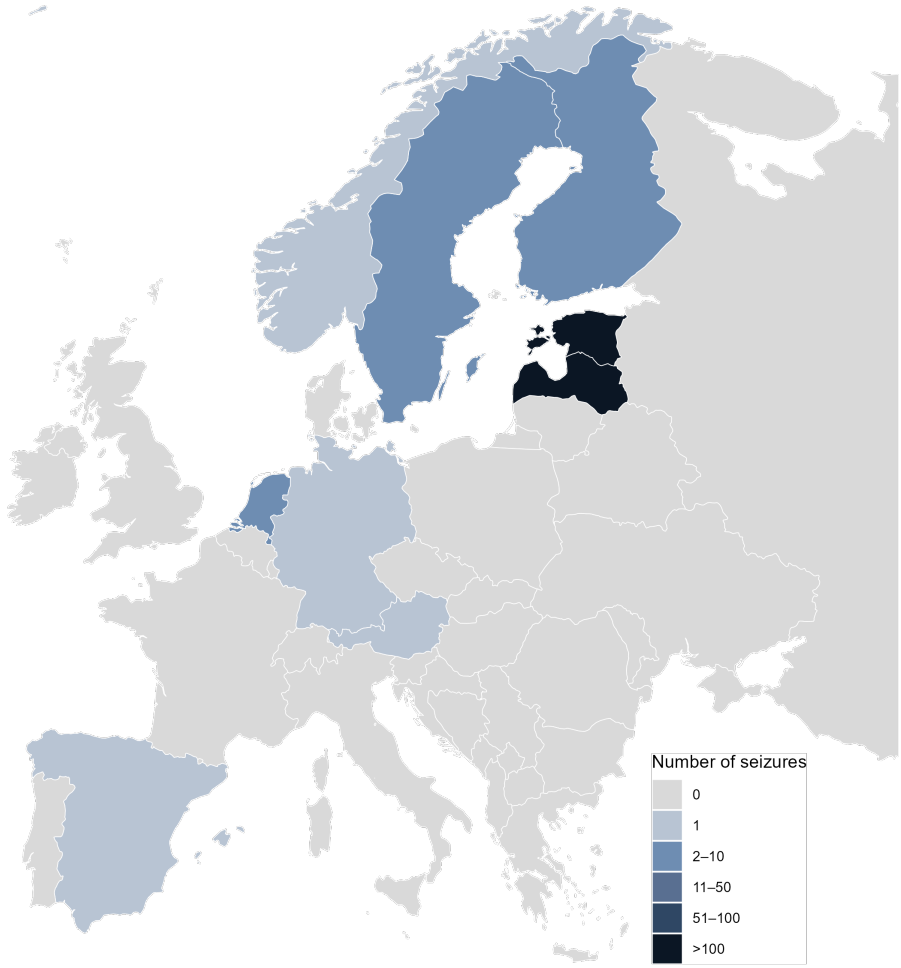
In addition, Sweden reported the seizure of a vaping device containing cychlorphine in 2025.

Finland, the Netherlands, Norway, and Spain reported five seizures involving a total of 37 cychlorphine blotters between 2025 and 2026. Where packaging information was available, the blotters were contained in plastic bags labelled as cychlorphine. Spain reported one case involving black-and-white stamp-like blotters labelled as cychlorphine. The Netherlands reported one case in which cychlorphine was reportedly purchased online and found in an envelope bearing Greek postage stamps; the product was labelled ‘Cychlorphine HCl’.

Among the 228 seizure cases reported between 2024 and 2026, cychlorphine was the only substance reported to be present in 117 cases (51%). It was found in combination with one or more other substances, including other opioids, in 99 cases (44%), while information on the presence of other substances was not available for the remaining 12 cases (5%).

Mixtures involving cychlorphine were first reported in 2025 and continued to be reported in 2026. In 2025, mixtures of cychlorphine and spirochlorphine were reported in 3 cases by Latvia, involving 0.9 kg of material and 0.28 mL of liquid.

Figure 2. Geographical distribution of seizures of cychlorphine



Note: Countries are classified according to the total number of seizures (0, 1, 2–10, 11–50, 51–100, >100). EU+2, 2024–2026.

Information from collected samples

Five Member States reported a total of 11 collected samples from the period June 2024 to May 2026: Austria (n=2), Estonia (n=5), France (n=2), Germany (n=1), and Greece (n=1). Six of the samples were submitted to drug checking services.

In nine cases, the samples were powders; one sample was a blotter; and in the remaining case, the physical form was not reported. Where colour was reported, the powders were described as white or beige. In one case reported by France, the person submitting the sample reported it as ‘cychlorphine’. In another case reported by Greece, the powder was

contained in a plastic bag labelled 'CYCHLORPHINE HCL, mixed 1:3, NOT FOR HUMAN CONSUMPTION'. In a further case reported by Austria the powder had reportedly been purchased online via the surface web.

Cychlorphine was the only substance detected in five cases. In five other cases, cychlorphine was detected alongside other substances, including etodezitramide (an orphine opioid), alpha-PVP, carfentanil, fentanyl and nortilidine. In one case, no information on the presence of other substances was reported.

Information from biological samples

Five Member States reported 51 biological samples, collected between August 2024 and March 2026, in which exposure to cychlorphine was confirmed: Estonia (n=43), Finland (n=1), Italy (n=1), the Netherlands (n=1), and Sweden (n=5). Nine samples were collected for criminal justice purposes, while the remaining 42 were associated with non-fatal poisonings or deaths discussed below.

4.1.2 Health problems

Acute poisonings

Two Member States reported 11 acute poisonings that occurred between October 2025 and March 2026 and in which exposure to cychlorphine was confirmed: Estonia (n=10) and Italy (n=1). Of these, two occurred in the last quarter of 2025 and nine in the first quarter of 2026.

In addition, 2 acute poisonings that occurred in September 2025 and involved probable exposure to cychlorphine were reported by two Member States: Germany (n=1) and the Netherlands (n=1). Five acute poisonings involving suspected exposure to cychlorphine were reported by three Member States: Germany (n=3), Sweden (n=1), and Spain (n=1). Of the suspected cases, one occurred in 2024, three in 2025, and one in 2026.

Deaths

Four Member States reported a total of 31 deaths that occurred between August 2024 and March 2026, in which exposure to cychlorphine was confirmed: Estonia (n=24), Sweden (n=5), Finland (n=1), and the Netherlands (n=1). One death occurred in August 2024, 16 from August to December 2025, and 14 from January to March 2026.

In 4 of the 31 cases (12.9%), cychlorphine was the only substance detected; the remaining cases involved polysubstance exposure.

Cychlorphine was assessed as having caused or contributed to death in 17 of 31 cases (54.8%); in the remaining cases, its causal role was not reported.

In addition, Germany reported 3 deaths in which exposure to cychlorphine was suspected: two occurred in December 2025 and one in January 2026.

Other

In at least two Member States (Estonia and Latvia), information, including findings from syringe residue analysis, indicates that cychlorphine is used by people who inject opioids. Injection as a route of administration is associated with additional harms, including transmission of blood-borne viruses, such as HIV and hepatitis B and C; bacterial and fungal infections; venous damage; and an elevated risk of nonfatal and fatal poisoning.

4.1.3 Social problems

No specific information is available on the social risks associated with the use of cychlorphine. Social harms are likely to resemble those associated with other opioids, such as heroin and fentanyl. Available information suggests that, in at least two Member States (Estonia and Latvia), use of cychlorphine is occurring within populations already affected by opioid dependence and its associated social harm (see Section 4.1.4).

4.1.4 Patterns of use

Detailed information on patterns of use of cychlorphine is limited. Further data are needed to characterise frequency of use, typical doses, and polysubstance use patterns.

In at least two Member States (Estonia and Latvia), information, including findings from syringe residue analysis, indicates that cychlorphine is used by people who inject opioids. In Latvia, cychlorphine was identified in 10 of 181 used syringes (6%) collected between November and December 2024. Preliminary data indicate that cychlorphine was identified in 111 of 200 syringes (56%) collected in Latvia between November and December 2025. In addition, cychlorphine has been seized in mixtures with other opioids, including other orphines, such as spirochlorphine, and nitazenes. Some seizures are indicative of street-level opioid supply.

The reported availability of other physical forms, such as blotters and liquids in a propylene glycol matrix, suggests that cychlorphine may be used by groups beyond people who inject opioids. In addition, there is potential for cychlorphine to be mis-sold as other drugs. In September 2025, Germany reported an acute non-fatal poisoning involving probable exposure to cychlorphine, linked to a product mis-sold online as a benzodiazepine pro-drug tablet. The extent of distribution, including whether other batches, vendors, or countries were affected, remains unknown.

4.2 Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction (Article 9 2(b))

4.2.1 Chemical description and names

Cychlorphine, also known as *N*-propionitrile chlorphine, is a synthetic piperidine benzimidazolone opioid, structurally related to the internationally controlled substances bezitramide ([10]) and brorphine ([11]).

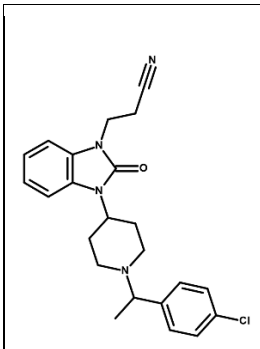
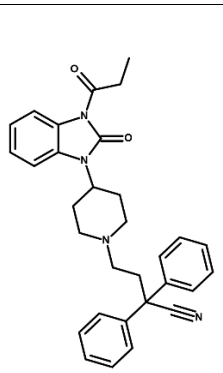
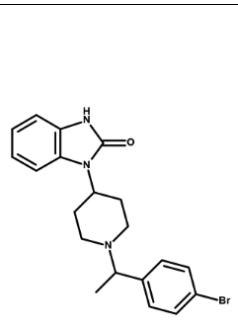
Benzimidazolone (‘orphine’) opioids differ from benzimidazole (‘nitazene’) opioids by a ketone moiety present in the 2-position of the benzimidazole group. Orphines also contain a piperidine ring linked to the benzimidazolone core, while nitazenes contain a benzyl group attached to the benzimidazole core.

Cychlorphine contains a stereogenic centre and therefore two possible enantiomers may exist.

The molecular structure, molecular formula and molecular mass of cychlorphine are provided in Figure 3. Information on bezitramide, and brorphine, is provided for comparison.

([10]) Listed in Schedule I of the 1961 Single Convention on Narcotic Drugs (1969).
([11]) Listed in Schedule I of the 1961 Single Convention on Narcotic Drugs (2022).

Figure 3. Molecular structure, molecular formula, and molecular mass of cychlorphine, bezitramide, and brorphine

			
Common name	cychlorphine (*N*-propionitrile chlorphine)	bezitramide	brorphine
Molecular Formula	$C_{23}H_{25}ClN_4O$	$C_{31}H_{32}N_4O_2$	$C_{20}H_{22}BrN_3O$
Molecular mass (g/mol)	408.92	492.61	400.31

Systematic (IUPAC) names:

3-(3-{1-[1-(4-chlorophenyl)ethyl]piperidin-4-yl}-2-oxo-2,3-dihydro-1*H*-1,3-benzimidazol-1-yl)propanenitrile

3-(3-{1-[(1*RS*)-1-(4-chlorophenyl)ethyl]piperidin-4-yl}-2-oxo-2,3-dihydro-1*H*-1,3-benzimidazol-1-yl)propanenitrile

Common names:

Cychlorphine

N-propionitrile chlorphine

Other chemical names:

3-[1-[1-(4-chlorophenyl)ethyl]-4-piperidinyl]-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-propanenitrile

3-[3-[1-[1-(4-chlorophenyl)ethyl]-4-piperidyl]-2-oxo-benzimidazol-1-yl]propanenitrile

3-(1-[1-(4-chlorophenyl)ethyl]piperidin-4-yl)-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-propanenitrile

3-[1-(*p*-chloro-α-methylbenzyl)-4-piperidyl]-2-oxo-1-benzimidazolinepropionitrile

1-[1-(4-chloro-phenyl)-ethyl]-4-[3-(2-cyano-ethyl)-2-oxo-1-benzimidazolinyl]-piperidine

Other names:

Cychlorophine

N-propionitrile chlorophine

Chemical Abstracts Service (CAS) registry numbers:

6449-60-1 (base)

16145-71-4 (hydrochloride salt)

IUPAC International Chemical Identifier Key (InChI Key):

SWWAVNFEFVMDAG-UHFFFAOYSA-N (base)

SLOVDXVMOHNKJL-UHFFFAOYSA-N (hydrochloride salt)

SWWAVNFEFVMDAG-KRWDZBQOSA-N (*S*-isomer)

SWWAVNFEFVMDAG-QGZVFWFLSA-N (*R*-isomer)

IUPAC International Chemical Identifier String (InChI string):

InChI=1S/C23H25ClN4O/c1-17(18-7-9-19(24)10-8-18)26-15-11-20(12-16-26)28-22-6-3-2-5-21(22)27(23(28)29)14-4-13-25/h2-3,5-10,17,20H,4,11-12,14-16H2,1H3 (base)

InChI=1S/C23H25ClN4O.ClH/c1-17(18-7-9-19(24)10-8-18)26-15-11-20(12-16-26)28-22-6-3-2-5-21(22)27(23(28)29)14-4-13-25;/h2-3,5-10,17,20H,4,11-12,14-16H2,1H3;1H (hydrochloride salt)

InChI=1S/C23H25ClN4O/c1-17(18-7-9-19(24)10-8-18)26-15-11-20(12-16-26)28-22-6-3-2-5-21(22)27(23(28)29)14-4-13-25/h2-3,5-10,17,20H,4,11-12,14-16H2,1H3/t17-/m0/s1 (*S*-isomer)

InChI=1S/2C23H25ClN4O/c2*1-17(18-7-9-19(24)10-8-18)26-15-11-20(12-16-26)28-22-6-3-2-5-21(22)27(23(28)29)14-4-13-25/h2*2-3,5-10,17,20H,4,11-12,14-16H2,1H3/t2*17-/m10/s1 (*R*-isomer)

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

CC(N1CCC(CC1)N2C(=O)N(CCC#N)c3ccccc23)c4ccc(Cl)cc4 (base)

Cl.CC(N1CCC(CC1)N2C(=O)N(CCC#N)c3ccccc23)c4ccc(Cl)cc4 (hydrochloride salt)

C[C@H](N1CCC(CC1)N2C(=O)N(CCC#N)c3ccccc23)c4ccc(Cl)cc4 (*S*-isomer)

C[C@@H](N1CCC(CC1)N2C(=O)N(CCC#N)c3ccccc23)c4ccc(Cl)cc4 (*R*-isomer)

4.2.2 Physical description

The hydrochloride salt of cychlorphine is a solid, reported to be soluble (≥10 mg/mL) in DMSO and methanol (Cayman Chemical, 2024).

The measured melting point for cychlorphine is 211.5–216.5 °C (Janssen, 1967).

A predicted octanol/water partition coefficient logP= 4.096±0.00 was determined ([12]) for cychlorphine, suggesting it is lipophilic and therefore physiologically available.

([12]) Octanol/water calculated using Advanced Chemistry Development (ACD/Labs) software (https://www.acdlabs.com/products/percepta-platform/physchem-suite/logp/)

To date, seizures and collected samples of cychlorphine reported to the EUDA have been identified in various physical forms, including beige and white powders, colourless liquids, blotters, and tablets.

Most identifications of cychlorphine reported to the EUDA do not specify whether the substance was detected as the free base or a salt form. In one case it was reported that the free base form of cychlorphine was identified in one liquid sample.

4.2.3 Methods and chemical precursors used for the manufacture or extraction

No information on the chemical precursors or manufacturing methods used to produce cychlorphine identified in Europe was reported by the EU Member States, Norway, or Türkiye. In addition, there is no information available on the chemical precursors or manufacturing methods used to produce cychlorphine identified on the European drug market.

The synthesis of cychlorphine is reported in a 1967 patent by Janssen Pharmaceuticals (Janssen, 1967). 1-Bromo-1-4(chloro-phenyl)-ethane is refluxed with 4-(2-oxo-1-benzimidazolinyl)-piperidine, sodium carbonate, potassium iodide and 4-methyl-2-pentanone, yielding 1-[1-(4-chloro-phenyl)-ehtyl]-4-(2-oxo-benzimidazolinyl)-piperidine. The product is then reacted with trimethylbenzylammonium hydroxide, tetrahydrofurane and acrylonitrile, yielding cychlorphine free base, which is converted to hydrochloride salt using gaseous hydrogen chloride.

General synthetic routes and precursors for benzimidazolone opioids are described in the literature (Kennedy *et al.*, 2018). Fluoronitrobenzene undergoes nucleophilic substitution with *N*-Boc-4-aminopiperidine. The nitro group is then reduced to an amino group and converted into the cyclic urea intermediate. The formed intermediate is Boc deprotected with trifluoracetic acid, followed by direct alkylation or reductive amination producing the desired analogues.

Other precursors and routes for the synthesis of cychlorphine are possible.

4.2.4 Identification and analysis

Analytical methods reported for the identification of cychlorphine in physical samples include: gas chromatography-mass spectrometry (GC-MS) (CFSRE, 2025), liquid chromatography-quadrupole time-of flight-mass spectrometry (LC-QTOF-MS) (CFSRE, 2024), liquid

chromatography-high resolution mass spectrometry (LC-HRMS) (Dugues *et al.*, 2026) and nuclear magnetic resonance (NMR) (Dugues *et al.*, 2026). Quantification of cychlorphine in physical samples can be carried by targeted LC-MS/MS using the method described in the literature (Dugues *et al.*, 2026).

A method for the separation and identification of 13 orphine opioids, including cychlorphine, using high-performance liquid chromatography with diode-array detection (HPLC-DAD), has been described (Gregerson, 2026).

No published methods for the identification and quantification of cychlorphine in biological samples were identified. However, analytical techniques established for brorphine may be applicable or adaptable. These include: liquid chromatography-quadrupole time-of flight-mass spectrometry (LC-QTOF-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Krotulski *et al.*, 2021; Grafinger *et al.*, 2021). Presumptive phase I metabolites of cychlorphine were identified using pooled human liver microsomes (HLMs) *in vitro* followed by liquid chromatography tandem mass spectrometry (LC-MS/MS) (Bassman *et al.*, 2025).

Based on observations for brorphine and other benzimidazolone opioids, cychlorphine concentrations in biological samples may fall in the nanogram to sub-nanogram range, requiring highly sensitive analytical instrumentation and low limits of detection (Krotulski *et al.*, 2021; Vandeputte *et al.*,2024).

Cychlorphine is commercially available as analytical reference material.

A reference standard for cychlorphine was included in the EUDA Analytical reference standards kit and were provided to the majority of national laboratories in the EUDA Network of Forensic and Toxicological Laboratories starting in October 2025. Supporting analytical data are also available on the European Database on New Drugs (EDND).

4.3 Pharmacological and toxicological description of the new psychoactive substance (Article 9 2(c))

Cychlorphine acts as a mu-opioid receptor (MOR) agonist (EUDA, 2026b). Recent *in vitro* and animal data suggest that cychlorphine may be more potent than fentanyl (EUDA, 2026b). Like other MOR agonists, cychlorphine produces dose-dependent acute effects in mice, including antinociception, bradycardia, and respiratory depression (EUDA, 2026b).

Pharmacological information remains limited. However, based on its mechanism of action, cychlorphine is expected to produce effects qualitatively similar to those of morphine, heroin,

and fentanyl, with respiratory depression representing the main poisoning risk (Kieffer, 1999; Romberg *et al.*, 2003; Pasternak and Pan, 2013; Pattinson, 2008; White and Irvine,1999). As with other opioid poisonings, respiratory depression is expected to be responsive to naloxone, although cychlorphine-specific clinical data is limited (Blundell *et al.*, 2024; Kim and Nelson, 2015; Sprague *et al.*, 2026; Stolbach *et al.*, 2026). Cychlorphine is also likely to have abuse liability and dependence potential (Herz, 1993).

4.4 Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance (Article 9 2(d))

Eighteen Member States and Norway ([13]) responded to Europol's request for information.

For some countries, no additional information on cychlorphine was available for inclusion in this report at the time of preparation.

A summary of the responses is provided below. Information corresponding to that reported separately by Reitox National Focal Points to EUDA is presented in the relevant sections of this report.

Austria reported that police were informed that cychlorphine is recently circulating as a street drug in the area bordering Slovenia. The also noted that cychlorphine had been identified in collected samples submitted to drug checking services (see section 4.1.1).

Finland reported three seizures of cychlorphine (see section 4.1.1).

Germany reported that cychlorphine has been seized in multiple incidents since 2025 and found in different forms (solid, liquid, tablets). One distribution method reported for cychlorphine was that it was mis-sold as benzodiazepine-prodrug tablets through online shops (see section 4.1.4). Germany noted that after poisonings linked to the tablets were reported, they were withdrawn from sale. Cychlorphine was also identified in a drug-use room in Düsseldorf in a sample analysed by a drug checking service (see section 4.1.1). Germany also reported a total of 4 deaths linked with cychlorphine. Two of the deaths were reported to be connected to the benzodiazepine-prodrugs tablets discussed above.

Norway reported 1 analytically confirmed and 4 non-analytically confirmed seizures of cychlorphine (see section 4.1.1).

([13]) Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, Portugal, Romania, Slovakia, and Sweden.

4.5 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 (Article 9(5))

The EMA reported that according to their searches, cychlorphine is not an active substance in:

- 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 ([14]), Regulation (EC) No 726/2004 ([15]) or Regulation (EU) 2019/6 of the European Parliament and of the Council ([16]);
- a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;
- a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;
- 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 in accordance with Article 112(1), point (c), of Regulation (EU) 2019/6;
- 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 ([17]).

([14]) 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). https://eur-lex.europa.eu/eli/dir/2001/83
([15]) 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).
([16]) 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).
([17]) 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. https://eur-lex.europa.eu/eli/dir/2001/20

4.6 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

ECHA, ECDC, and EFSA reported to the EUDA that they do not hold any data or information on cychlorphine relevant to their mandates. The only known legitimate use of cychlorphine is as analytical reference material for clinical and forensic casework and scientific research. No information currently suggests that it is used for any other legitimate purpose.

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

Sixteen Member States reported that cychlorphine is not subject to restrictive measures at national level: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, France, Greece, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain.

Norway also reported that cychlorphine is not subject to restrictive measures at national level.

Eleven Member States reported that cychlorphine is subjected to restrictive measures at national level: Denmark, Estonia, Finland, Germany, Hungary, Italy, Ireland, Latvia, Lithuania, Poland, and Sweden.

Türkiye also reported that cychlorphine is subject to restrictive measures at national level.

Drug control legislation

Seven Member States reported that cychlorphine is controlled under drug control legislation: Denmark, Estonia ([18]), Finland ([19]), Italy ([20]), Latvia ([21]), Lithuania ([22]), and Sweden ([23]).

([18]) https://www.ravimiamet.ee/uudised/narkootiliste-ja-psuhhotroopsete-ainete-nimekirja-lisati-uued-ained-0, as of 3 February 2026
([19]) https://www.finlex.fi/fi/lainsaadanto/2008/543#OT5, as of 29 December 2025
([20]) https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:decreto.del.presidente.della.repubblica:1990-10-09;309!vig= ; https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=109213, as of 24 November 2025
([21]) https://likumi.lv/ta/en/en/id/50539-on-the-procedures-for-the-coming-into-force-and-application-of-the-criminal-law, as of 2025
([22]) https://www.e-tar.lt/portal/en/legalAct/TAR.7B3B40DCD13A/JDbXNjONfc, as of 17 June 2025
([23]) https://www.riksdagen.se/sv/dokument-och-lagar/dokument/svensk-forfattningssamling/forordning-19921554-om-kontroll-av-narkotika_sfs-1992-1554/, as of 6 May 2025. Previously, cychlorphine was regulated as goods dangerous to health (entered into force 10 December 2024)

New psychoactive substance legislation

Four Member States reported that cychlorphine is controlled under new psychoactive substance legislation: Germany ([24]), Hungary ([25]), Ireland ([26]), and Poland ([27]).

Türkiye also reported that cychlorphine is controlled under New Psychoactive Substance control legislation ([28]).

4.8 Information on whether the new psychoactive substance is currently or has been under assessment within the United Nations system

On 4 May 2026, the World Health Organization informed the EUDA that cychlorphine is not currently under assessment, nor has it previously been assessed within the United Nations system.

5. Analysis and assessment

3-(3-{1-[1-(4-Chlorophenyl)ethyl]piperidin-4-yl}-2-oxo-2,3-dihydro-1*H*-1,3-benzimidazol-1-yl)propanenitrile, commonly known as cychlorphine, is a piperidine benzimidazolone and synthetic opioid belonging to the orphine opioids, a group of related new synthetic opioids that includes bezitramide and brorphine. Cychlorphine is monitored by the EUDA as a new psychoactive substance through the European Union Early Warning System (EWS), in accordance with Regulation (EU) 2023/1322.

Cychlorphine is structurally related to bezitramide and brorphine, both of which are controlled under Schedule I of the United Nations 1961 Single Convention on Narcotic Drugs because of the public health and social risks they pose. Given this structural relationship and its opioid activity, including indications of potency exceeding that of fentanyl, cychlorphine may be expected to produce similar opioid effects and associated harms. Among these, respiratory depression is the main acute poisoning risk. As with other opioids, cychlorphine-related respiratory depression is expected to be responsive to naloxone, although cychlorphine-specific clinical data are limited.

([24]) https://dserver.bundestag.de/brd/2025/0534-25.pdf, as of 9 October 2025
([25]) https://njt.hu/jogszabaly/2022-78-20-0A, as of 25 July 2025
([26]) https://www.irishstatutebook.ie/eli/2010/act/22/enacted/en/pdf
([27]) https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20051791485/U/D20051485Lj.pdf, as of 27 November 2025
([28]) Law No. 2313 on the Control of Narcotic Substances as of 10 January 2026

Cychlorphine was formally notified by the EUDA as a new psychoactive substance by the EUDA in February 2025, following a seizure in Sweden in August 2024. However, the substance may have been on the market in Europe since at least June 2024. As of May 2026, it has been identified in 11 Member States and Norway.

It is important to note that cychlorphine may be under-detected on the drug market and in serious adverse events in Europe, as the substance is not routinely screened for in some laboratories.

Although distribution patterns remain poorly characterised, the limited available information suggests that cychlorphine is sold under its own name as a ‘legal’ substitute for controlled opioids, and it may also be mis-sold as — or mixed with — controlled opioids themselves.

Available information indicates that cychlorphine is used by people who inject opioids, and injecting use has been reported in two Member States. The substance has also been reported in other forms, including blotters and liquids, but the relative scale of different routes of administration and user groups is unknown. Where cychlorphine is injected, additional harms may occur, including risks from transmission of blood-borne viruses such as HIV.

During the 2024–2026 reporting period, seizures of cychlorphine were reported in increasing numbers from 2025 onwards in Europe. In total, 228 seizures were reported by eight Member States and Norway. The seizures involved several physical forms, with the main reported quantities comprising approximately 6.5 kilograms of material and 4 litres of liquid. Approximately 0.9 kg of the material seized consisted of a mixture containing cychlorphine and another orphine opioid, spirochlorphine, which is being assessed in a parallel initial report.

Since 2025, harms associated with cychlorphine have also been increasingly reported in Europe, including acute poisonings and deaths. A total of 11 cases of acute poisoning with confirmed exposure to cychlorphine have been reported by two Member States. In addition, a total of 31 deaths with confirmed exposure to cychlorphine have been reported by four Member States. In at least 17 of these deaths, the substance was reported to have caused or contributed to the fatal outcome; in 4 cases, it was the sole substance detected.

Since 2024, a marked increase has been observed in the number of orphine opioids identified on the European drug market, with nine new substances reported, including cychlorphine. The increased availability of orphines may partly reflect the introduction of China's generic control of nitazene opioids in July 2025. This measure appears to have reduced nitazene availability, with cychlorphine and other orphines, such as spirochlorphine, emerging as replacements.

Based on information reported to the EUDA, there is evidence of criminal acts involving cychlorphine in Europe, including trafficking and supply offences. However, there is currently limited information on the involvement of organised criminal groups in its manufacture, trafficking, and distribution.

Based on the available information, cychlorphine is not used as an active substance in any authorised medicinal product for human or veterinary use in Europe, nor is it used in any extemporaneously prepared medicinal product or investigational medicinal product.

Aside from limited use as an analytical reference standard and in scientific research, there is currently no information suggesting that cychlorphine is used for other legitimate purposes.

Cychlorphine is subject to restrictive measures in 11 Member States, as well as Türkiye, and is not subject to restrictive measures in the remaining 16 Member States and Norway.

Cychlorphine has not been assessed, nor is it currently under assessment, by the United Nations system.

The available information shows that cychlorphine availability and reported harms have increased significantly in the European Union since 2025. The EUDA considers that these findings indicate potential health and social risks at Union level and therefore concludes that the risks posed by the use, manufacture and distribution of the substance, and the involvement of criminal groups, could be assessed through a risk assessment procedure as specified in Article 10 of Regulation (EU) 2023/1322.

The EUDA will continue to intensively monitor cychlorphine and will ensure that new information is provided to the Member States, Europol, the Commission, and the EMA through the European Union Early Warning System (EWS) in a timely manner.

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The European Union Drugs Agency (EUDA) is the leading authority on illicit drugs in Europe. Based in Lisbon, Portugal, we provide independent scientific evidence and analysis on all aspects of this constantly changing threat to individual lives and wider society. Our work contributes to EU and national policies to protect Europe's citizens from drug-related harms. We are an agency of the European Union.

More information

- EUDA Early Warning System on NPS
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