

Seventh addendum to the ACMD report on the use and harms of 2-benzyl- benzimidazole ('nitazene') and piperidine benzimidazolone ('brorphine-like') opioids

30 April 2026

Background

In July 2022, the ACMD published its advice on 2-benzyl benzimidazole (nitazene) and piperidine benzimidazolone ('brorphine-like') opioids. The report recommended that a number of named materials should become controlled under the Misuse of Drugs Act (MDA) 1971. The ACMD also recommended the introduction of a generic control to address emerging and potential nitazene variants. The Council also advised that, should evidence emerge of any variants of brorphine, similar controls should be considered for piperidine benzimidazolones, requiring a similar consultation. Since the report's publication, the ACMD have published a series of addenda recommending the control of additional nitazene variants and adjusting the scope of the proposed nitazene generic control.

The piperidine benzimidazolone ('orphine') group of drugs, were originally developed as potential analgesics by Paul Janssen in the 1960s. However, his parallel work on fentanyl took precedence and only one orphine variant, bezitramide, was commercially developed and marketed as 'Burgodin'.

Bezitramide was an orally active narcotic analgesic, with a potency greater than morphine, a slow onset and long duration. In 1969, it was placed in Schedule 1 of the 1961 Convention on Narcotic Drugs. Although bezitramide is listed by name in the UN Convention, it acts *in-vivo* as a pro-drug for its active metabolite, despropionylbezitramide and this is not currently UN listed [Vandeputte et al, 2024]. It is understood that, following a number of fatalities, bezitramide was withdrawn from the market in 2004.

Janssen had explored a wide range of orphine variants for their analgesic activity in the 1960s and his work has subsequently been expanded by others. Information about synthesis, mu opioid binding affinities and effects is therefore available in patents, scientific papers and internet discussion groups.

Brorphine, a brominated variant of orphine, was described in the literature in 2018 and shortly afterwards appeared as an opioid New Psychoactive Substance (NPS). In 2022, this too was added to Schedule 1 of the 1961 UN Convention. Both bezitramide and brorphine are named Class A drugs in the United Kingdom's Misuse of Drugs Act 1971.

Other orphine variants are currently being explored by NPS suppliers seeking to develop opioid NPS as alternatives to fentanyl and nitazenes as these are increasingly coming under international control. Some, like cyclochlorphine and spirochlorphine which have been detected in the USA, Europe and the UK, are reported to have opioid agonist potencies which are similar to or exceed that of fentanyl, while the potencies of others, such as, etodezitramide and cyetodezitramide, may approach that of carfentanil.

Published information on orphines is currently limited. However, based on reported *in-vitro* binding studies and some historic animal testing results, some structural themes can be deduced [Kennedy et al, 2018]. These include the presence of a small alkyl substituent on the benzylic carbon being required for potency, while replacement of the benzylic carbon by a longer chain significantly reduces mu opioid activity. Certain other modifications can be seen to impart particular potency, such as attachment of a cyanoethyl group to the benzimidazolone 3-position nitrogen (materials of this type being referred to as "Cy-" compounds) or of a cyano or a propionyl group ("Eto-" compounds) to the diphenylpropyl group of bezitramide-type materials. At the extremes, etospirotramide (R5260) has been suggested to be equipotent to 3-methylfentanyl while cyetodezitramide is alleged to be so potent as to have once been considered for commercialisation as a euthanising reagent for stranded whales.

Other more-distantly related materials with mu opioid agonism were also explored by Janssen, but have not yet emerged as opioid NPS and are not considered below.

Janssen also developed a number of structurally-related materials with much reduced opioid activity but with characteristics making them useful as anti-psychotic medications, such as Benperidol and Droperidol. Any generic control on orphine-like materials therefore needs to be sufficiently specific to capture materials with potentially problematic opioid agonist characteristics while avoiding those with other properties of pharmaceutical interest.

Prevalence of Orphines

United Kingdom

The ACMD have recently been made aware of bromphine-like materials appearing in the UK or European mainland drug markets. The following compounds are currently not controlled via the MDA but, as potent psychoactive substances would be captured by the Psychoactive Substances Act 2016 (PSA):

- Chlorphine
- Cychlorphine (N-propionitrile chlorphine)
- Spirochlorphine (R-6890)
- 5,6-Dichloro desmethylchlorphine (SR-17018)
- Etodezitramide
- Spirobromphine
- 5,6-dichlorobromphine (SR 14968)

The National Crime Agency (NCA) and Office for Health Improvement and Disparities (OHID) have reported that in England alone there have been more than 15 confirmed deaths in which orphines were involved since the spring of 2025. The 2 compounds involved were reported to be cychlorphine and spirochlorphine.

The National Programme on Substance Use Mortality (NPSUM), which analyses data from coroner reported inquests in England and Wales, identified 14 orphine detections from data collated through submitted case reports. Of these, 11 detections involved cyclophine, while 3 involved chlorphine. Further details of these cases are not available and overlap with the NCA data cannot be excluded.

International

Since 2024, the United Nations Office on Drugs and Crime (UNODC) has received 206 reports from multiple countries, documented through its Early Warning Advisory programme, of drug samples containing orphine compounds. In addition, the UNODC has documented 60 post-mortem toxicology cases from the United States involving cyclophine specifically.

Orphine and spirorphine structures

The drugs commonly referred to as 'orphines' are of two main types, those like orphine itself, which include a benzimidazol-2-one core and those like spirorphine, which include a triaspiro[4.5]decanone core (see note below regarding the structure and nomenclature of

'spiro' variants). Bezitramide-like materials are essentially orphines with a 3,3-diphenylpropyl group attached to the piperidinyl nitrogen, echoing the structure seen in methadone.

Orphine-like materials

The orphine-like materials have three component units within their structures. These are a benzimidazolone core, a 4-piperidine ring attached to a nitrogen atom of the benzimidazolone core and a benzyl group attached to the nitrogen of the 4-piperidine unit. Each of these units can be modified in a variety of ways. Amongst the substitutions present in materials which have been reported to be opioid agonists are:

- The phenyl ring within the benzimidazolone core substituted by groups such as alkyl or halogens
- The second nitrogen atom of the benzimidazolone core substituted by alkyl, cyanoalkyl (cyanoethyl imparting particular additional potency) or acyl
- The phenyl ring of the benzyl group substituted by alkyl, alkoxy, halogens or haloalkyl
- The methanoic carbon of the benzyl group substituted by a small alkyl group, typically methyl
- The benzyl group being replaced by 3-cyano-3,3-diphenylpropyl or 4-alkyl-4-oxo-3,3-diphenylbutyl

Spirorphine-like materials

The spirorphine-like materials also have a three-component structure. These are a 1,3,8-triazaspiro[4.5]decan-4-one core, a phenyl group at the 1- position nitrogen of the core and a benzyl group attached to the nitrogen at the 8- position. Modifications reported include:

- The nitrogen at the 3- position of the core substituted by a small alkyl group
- The phenyl ring of the benzyl group substituted by alkyl, alkoxy, halogens or haloalkyl
- The methanoic carbon of the benzyl group substituted by a small alkyl group, typically methyl
- The benzyl group being replaced by 3,3-diphenylpropyl, 3-cyano-3,3-diphenylpropyl or 4-alkyl-4-oxo-3,3-diphenylbutyl

Possible wording for generic controls

Although related and including materials reported to have similar pharmacology at the mu-opioid receptor, the core structures of the two groups are significantly different.

The recently updated German Neue-psychoaktive-Stoffe-Gesetz (NpSG; New Psychoactive Substances Act) regulations have a single generic covering both types of materials, based around two structural diagrams, showing the two core structures followed by a listing of the various substitutions onto those cores which merit control [Germany-NpSG, 2026]. A similar approach using only words for insertion into UK legislation would be rather lengthy, and potentially confusing, so a pair of controls is instead proposed.

Notably, the German generic does not cover bezitramide-related materials where there are 3,3-diphenylpropyl variants attached to the piperidinyl nitrogen. This is significant as despropionylbezitramide is known to be the active metabolite for bezitramide. In addition, one of the materials being advertised on several European NPS websites, and which has already been identified in the UK by the Welsh Emerging Drug & Identification of Novel Substances programme (WEDINOS), is etodezitramide (R4837) which is reported to have a

potency many times that of fentanyl. The related cyetodezitramide can be expected to demonstrate even greater potency.

The German generic also covers feasible variants which have not yet been reported. These include modification of the phenyl ring of the benzimidazolone core of orphines or the phenyl ring attached to the spirorphine core by the addition of the 'bridge' structures methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy. Given the inherent potency of the orphine/spirorphine structures, these materials, should they appear, are likely to retain significant activity. These possibilities are addressed in the suggested generics below but may be regarded as unnecessary at this stage. In addition, substitutions onto the various phenyl rings by alkylsulphonyl and trialkylsilyl groups are included in the German control, probably in light of legislation-avoiding variants of other drugs which have been encountered in Germany.

The opioid activity of these materials is likely to result in them becoming controlled as Class A materials, similar to the classification of other opioid NPS such as fentanyls and nitazenes. As bezitramide and broporphine are already listed as Class A drugs in sub-para (a) of Part 1 of Schedule 2 of the MDA and assuming that some other orphines which have already been encountered are to be recommended for control as named compounds in the ACMD's report, an initial exclusion clause will be necessary to avoid duplication.

A Class A generic control for orphine-like materials could therefore be worded as:

“Any material (not being a compound for the time being specified in sub-paragraph (a) above) structurally derived from 1-(1-benzylpiperidin-4-yl)-1,3-dihydro-benzimidazol-2-one by modification in any of the following ways:

- 1. By substitution to any extent on the phenyl ring of the benzimidazolone core by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 2. By substitution at the 3- position nitrogen of the benzimidazolone core by alkyl, cyanoalkyl or acyl*
- 3. By substitution to any extent on the phenyl ring of the benzyl group by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 4. By substitution on the methylene group of the benzyl group by alkyl containing up to three carbon atoms*
- 5. By replacement of the benzyl group by a 3,3-diphenylpropyl, a 3-cyano-3,3-diphenylpropyl or a 4-alkyl-4-oxo-3,3-diphenylbutyl group.”*

The matching Class A generic control of spirorphine-like materials could be worded as:

“Any material (not being a compound for the time being specified in sub-paragraph (a) above) structurally derived from 8-benzyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one by modification in any of the following ways:

- 1. By substitution of the nitrogen at the 3- position of the triazaspiro core by alkyl*
- 2. By substitution to any extent on the phenyl ring of the benzyl group by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 3. By substitution on the methylene group of the benzyl group by alkyl containing up to three carbon atoms*
- 4. By substitution to any extent on the 1-phenyl ring by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 5. By replacement of the benzyl group by a 3,3-diphenylpropyl, a 3,3-diphenyl-3-cyanopropyl or a 4-alkyl-4-oxo-3,3-diphenylbutyl group.”*

The proposed generics are lengthy and broad. Should consultation reveal these generics capture any licensed pharmaceutical, the introductory text would have to be expanded to “(not being [substance A], [substance B] or a compound...”

Note: Use of the ‘Spiro’ nomenclature for compounds containing joined rings

In the IUPAC nomenclature for joined rings, when two ring structures are joined at a single shared atom, the shared atom is referred to as the ‘spiro’ atom. To clarify how the rings are joined, a ‘von Baeyer’ numbering system is applied. This counts the number of atoms, other than the shared spiro atom, in each of the two rings and these two numbers are then reported as a term in square brackets separated by a full stop, with the number of atoms in the smaller ring first.

In spirorphine, which has a core containing a five membered ring sharing an atom with a six membered ring, so that there is a total of ten atoms in the joined rings, the base term for the central core structure, ignoring the hetero atoms, is therefore “spiro[4.5]decane”. As the spirorphine core rings contain three nitrogen hetero atoms, this then becomes “triazaspiro[4.5]decane”. To indicate where the nitrogen atoms are situated within the rings, the atom numbering around the core follows the same sequence, that is, counting around the smaller ring first, starting at the atom adjacent to the spiro atom and including the ‘spiro’ atom so, in spirorphine, this becomes “1,3,8-triazospiro[4.5]decane”.

The full spirorphine structure also contains a phenyl group at the 1- position, an oxygen at the 4- position, and a 1-phenylethyl group at the 8- position, so the complete nomenclature for spirorphine becomes 1-phenyl-8-(1-phenylethyl)-1,3,8-triazaspiro[4.5]decan-4-one.

Options for legislative control

It is the view of the ACMD from the evidence collected and presented in this report that, orphine and spirorphine compounds are drugs that are present in the UK illicit drug market and that their use is having harmful effects. The ACMD considers that the risk to the population from these recently emerging compounds is sufficiently great that urgent steps are required to protect public health. In developing this generic, the ACMD consulted the Medicines and Healthcare products Regulatory Agency (MHRA) regarding information on these compounds medical use. The MHRA have confirmed that they have no records of any clinical trials, unlicensed imports or pending licensing applications for the orphine and spirorphine compounds detailed in this report. In addition, the wording of the generic definitions were reviewed by external stakeholders specialising in chemical regulations. Currently, as these compounds are potent psychoactive substances, they will be subject to the Psychoactive Substances Act 2016, but given the threat to public health, the ACMD and its NPS Committee have considered the options for actions to further control these substances to reduce this threat. The possible options proposed are:

- Option 1: Inclusion of 7 named compounds to Class A of the Misuse of Drugs Act 1971, and Schedule 1 of the Misuse of Drugs Regulations 2001 AND inclusion of two generic definitions to cover piperidine benzimidazolone (‘brorphine-like’) opioids into the Misuse of Drugs Act 1971, without further consultation, to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids, such as nitazenes. As these materials have no medical use, it is recommended that they should be placed in

Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001;

- Option 2: Inclusion of 7 named compounds to Class A of the Misuse of Drugs Act 1971, and Schedule 1 of the Misuse of Drugs Regulations 2001 AND inclusion of two generic definitions to cover piperidine benzimidazolone ('bromphine-like') opioids into the Misuse of Drugs Act 1971 following further consultation on the proposed generic wording consistent with the classification of other potent opioids such as nitazenes. As these materials have no medical use, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001. This consequence of further consultation would delay when these compounds could be controlled under the MDA;
- Option 3: Enactment of a temporary class drug order (TCDO) for the seven named compounds pending the enactment of Option 1 or Option 2. This could be enacted more rapidly and would enable greater penalties for the manufacture, importation and sale of these compounds. There is a potential unintended consequence of the enactment of the TCDO in regard to possession in a custodial setting. As these compounds are currently subject to the PSA 2016, their possession in a custodial setting would be an offence. Since the PSA 2016 excludes compounds regulated by the MDA, the enactment of a TCDO for these compounds to control these substances would mean that possession in a custodial setting would no longer be an offence. The ACMD considered this issue in 2019 and concluded at that time that the absence of a specific offence in custodial settings was not a significant factor influencing the use of novel psychoactive substances (NPS) within such environments [ACMD, 2019]. However, this assessment was undertaken prior to the subsequent increase in the availability of novel synthetic opioids. It is therefore unclear whether the conclusions reached in the 2019 review remain applicable to the current custodial drug market.

Recommendations

The ACMD considers that there are established harms associated with orphine and spirorphine compounds and therefore recommends urgent control under the Misuse of Drugs Act 1971 to protect public health.

Revised Recommendation 1 to ACMD report on the use and harms of 2-benzyl benzimidazole ('nitazene') and piperidine benzimidazolone ('brorphine-like') opioids:

In addition to Recommendation 1, the following compounds should be added **as a matter of urgency** to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids. As these materials have no medical use it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001.

- Chlorphine
- Cychlorphine (N-propionitrile chlorphine)
- Spirochlorphine (R-6890)
- 5,6-Dichloro desmethylchlorphine (SR-17018)
- Etodezitramide
- Spirobrorphine
- 5,6-dichlorobrorphine (SR 14968)

Lead: Home Office

Measure of outcome: The inclusion of the listed compounds in Class A of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001 and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001 **as a matter of urgency**.

Revised Recommendation 3 to ACMD report on the use and harms of 2-benzyl benzimidazole ('nitazene') and piperidine benzimidazolone ('brorphine-like') opioids

Inclusion of two generic definitions for piperidine benzimidazolone ('brorphine-like') opioids **as a matter of urgency** into the Misuse of Drugs Act 1971.

Materials covered by both generics should be added to Class A of the Misuse of Drugs Act 1971, consistent with the classification of other potent opioids. As these materials have no medical use, it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001. The proposed wording for the generic for addition to the Misuse of Drugs Act is as follows:

“Any material (not being a compound for the time being specified in sub-paragraph (a) above) structurally derived from 1-(1-benzylpiperidin-4-yl)-1,3-dihydro-benzimidazol-2-one by modification in any of the following ways:-

- 1. By substitution to any extent on the phenyl ring of the benzimidazolone core by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 2. By substitution at the 3- position nitrogen of the benzimidazolone core by alkyl, cyanoalkyl or acyl*
- 3. By substitution to any extent on the phenyl ring of the benzyl group by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 4. By substitution on the methylene group of the benzyl group by alkyl containing up to three carbon atoms*
- 5. By replacement of the benzyl group by a 3,3-diphenylpropyl, a 3-cyano-3,3-diphenylpropyl or a 4-alkyl-4-oxo-3,3-diphenylbutyl group.”*

The matching Class A generic control of spirorhine-like materials is as follows:-

“Any material (not being a compound for the time being specified in sub-paragraph (a) above) structurally derived from 8-benzyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one by modification in any of the following ways:-

- 1. By substitution of the nitrogen at the 3- position of the triazaspiro core by alkyl*
- 2. By substitution to any extent on the phenyl ring of the benzyl group by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 3. By substitution on the methylene group of the benzyl group by alkyl containing up to three carbon atoms*
- 4. By substitution to any extent on the 1-phenyl ring by alkyl, alkoxy, halogen, haloalkyl, methylenedioxy, ethylenedioxy, ethyleneoxy or vinylenoxy*
- 5. By replacement of the benzyl group by a 3,3-diphenylpropyl, a 3,3-diphenyl-3-cyanopropyl or a 4-alkyl-4-oxo-3,3-diphenylbutyl group.”*

Lead: Home Office.

Measure of outcome: The inclusion of two generic definitions for piperidine benzimidazolone ('rorphine-like') opioids in Class A the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001 and the Misuse of Drugs (Designation) (England, Wales, and Scotland) Order 2015, Northern Ireland 2001 **as a matter of urgency**.

Recommendation for Control of specific named substances through the enactment of a temporary class drug order (TCDO).

If control under the Misuse of Drugs Act 1971, as proposed in revised Recommendations 1 and 3 above, cannot be expedited due to parliamentary or other time constraints, then the ACMD advises, that pursuant to Section 2B(1)(b) and (6) of the Misuse of Drugs Act 1971, the following compounds be subjected to a temporary class drug order:

- Cychlorphine (N-propionitrile chlorphine)
- Spirochlorphine (R-6890)
- 5,6-Dichloro desmethylchlorphine (SR-17018)
- Etodezitramide
- Spirobrorphine
- Chlorphine
- 5,6-dichlorobrorphine (SR 14968)

Lead: Home Office.

Measure of outcome: Enactment of a TCDO for these named compounds **as a matter of urgency**.

REFERENCES

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3. Federal Ministry of Justice (Germany) (2026). Neue-psychoaktive-Stoffe-Gesetz (NpSG): Annex 1, Section 9. https://www.gesetze-im-internet.de/npsg/anlage_1.html
4. Advisory Council on the Misuse of Drugs (ACMD) (2019). Advice on the future use and purpose of Temporary Class Drug Orders. Home Office, 18 October 2019.