

# ACMD

## Advisory Council on the Misuse of Drugs

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Rt. Hon. Priti Patel MP  
Home Secretary  
2 Marsham Street  
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18<sup>th</sup> July 2022

Dear Home Secretary,

**Re: ACMD Report - a review of the evidence on the use and harms of 2-benzyl benzimidazole ('nitazene') and piperidine benzimidazolone ('brorphine-like') opioids**

Two separate ministerial commissions on Isotonitazene and Brorphine requested ACMD to provide advice on the appropriate classification and scheduling of these compounds under the Misuse of Drugs Act 1971 and associated Regulations. This was required to be in line with international controls of those compounds, as they were recently added to the relevant schedules of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol and the Convention on Psychotropic Substances of 1971.

The ACMD has therefore written the attached report describing the use and harms of 2-benzyl benzimidazole ('nitazene') opioids, (including isotonitazene) and piperidine benzimidazolone opioids (including brorphine). The ACMD is pleased to enclose this report with recommendations on the classification and scheduling of isotonitazene, brorphine and related substances, following a thorough review of the evidence available and utilising the expertise of the ACMD Novel Psychoactive Substances Committee (NPSC) members.

The report demonstrates that both groups of compounds include examples that have highly potent heroin-like effects where use carries a high risk of potentially fatal overdose. Because these compounds have the potential to cause severe harm and pose a significant threat to the public, the ACMD has recommended that they should be controlled under the Misuse of Drugs Act 1971 as Class A compounds. They should be listed in Schedule 1 of the Misuse of Drugs Regulations, as they currently have no known legitimate use. Following consultations by the Home Office, and in view of the risk to the public, the ACMD recommends that 10 specific substances (including isotonitazene and buporphine) are controlled by name as soon as possible. There is, however, a risk of further related compounds being developed, so a generic chemical description allowing the wider control of 2-benzyl benzimidazole opioids is also suggested in the report. The ACMD recommends that this generic description should be used in due course, following a consultation with relevant stakeholders, including academia and the chemical and pharmaceutical industries.

In this report the following conclusions were reached:

1. 2-Benzyl benzimidazole and piperidinyl benzimidazolone opioids include compounds with very high potency. Although direct evidence of the health harms of these newly emerging groups of drugs is limited, these are likely to reflect those of other potent opioids and the clinical data described to date is consistent with this. Thus, the recent availability of these compounds presents a significant potential threat to public health.
2. There is evidence of the recent emergence of several new synthetic opioids from these groups into illicit drug markets internationally, including isotonitazene, N-pyrrolidino-etomidazene, butomidazene, metomidazene, protonitazene, etodesnitazene, flunitazene, metodesnitazene and buporphine. Many cases of severe or fatal toxicity involving these compounds have been described in Europe and North America.
3. 2-Benzyl benzimidazole opioids have also been detected in the UK, where there were at least 24 fatalities involving isotonitazene and 3 involving N-pyrrolidino etomidazene during 2021. In these cases, it cannot be established that 2-benzyl benzimidazole opioids were the sole cause of death, as other compounds were also commonly detected, but they are likely to have made an important contribution in many cases.

4. The total number of fatalities recorded as associated with new synthetic opioids (NSO) is likely to be an underestimate as not all drug-related deaths are investigated using methods sufficiently sensitive to detect the involvement of these compounds. For the same reason, it took several weeks for the involvement of isotonitazene in drug-related fatalities in the UK to be recognised. Further cases may emerge if retrospective analyses are conducted. More detailed sample analysis is needed to establish the role of emerging NPS in individual drug-related deaths, as well as to provide timely information on the cause of clusters of drug deaths. Such analysis, however, is costly and adequate funding would be required.
5. The involvement of NSO will not be recognised in most non-fatal cases of drug-related toxicity because detailed sample analysis is not a component of usual clinical care. Several non-fatal cases of exposure have, however, been reported involving isotonitazene and N-pyrrolidino etonitazene. In some cases, the opioid antagonist naloxone has been used with subsequent clinical improvement, consistent with experimental evidence that it antagonises the effects of 2-benzyl benzimidazole opioids as it does those of established opioids.
6. Evidence collected in the UK suggests that isotonitazene may be an adulterant in heroin or cocaine preparations and people using these are likely to be unaware of their exposure to isotonitazene. It remains uncertain if contamination is done deliberately to enhance the effects of the drug product or if in some cases it results from accidental cross-contamination, such as from using the same equipment for cutting different drug products.
7. The piperidinyl benzimidazolone opioid buprenorphine has been involved in multiple fatalities in other countries but has been infrequently detected in the UK, although numbers may be underestimates as analyses used to investigate fatal cases may not be able to detect this compound. There is currently no evidence of the misuse of other compounds from this group.
8. With the exception of etonitazene and clonitazene, 2-benzyl benzimidazole opioids are not controlled via the Misuse of Drugs Act 1971, although they are subject to the Psychoactive Substances Act 2016. This is also the situation for the piperidinyl benzimidazolone opioids including buprenorphine. This position is not consistent with that of other potent opioids including heroin, morphine and fentanyl, which are

Class A drugs of misuse. The UK is obliged to control isotonitazene, metonitazene and buprenorphine now that they are listed in schedule I of the United Nations Single Convention on Narcotic Drugs of 1961, as amended by the 1972 Protocol, but control of other unlisted 2-benzyl benzimidazole or piperidinyl benzimidazolone opioids that have been detected in the UK or elsewhere should also be considered.

9. No legitimate medical uses of 2-benzyl benzimidazole opioids have been identified in the UK or internationally, so placement in schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) would be consistent with the current legal status for other opioids that do not have a legitimate medical use, such as MT-45, U-47,700 and non-pharmaceutical fentanyl analogues. Etonitazene and clonitazene are currently listed in schedule 2 – this appears to be historic as they may have been considered as having possible therapeutic value in the past. No legitimate medical use has since been identified, however, so listing these in schedule 1 is appropriate and consistent with the position of other similar compounds.
10. To date almost all UK evidence implicates isotonitazene and N-pyrrolidino etonitazene, although metonitazene, etodesnitazene, butonitazene and buprenorphine have also been detected. Other 2-benzyl benzimidazole opioids detected internationally are very likely to appear in the UK and could cause substantial health harms, so monitoring for the emergence of these compounds and their health harms in the UK remains important. In view of the potential risks they pose to public health, pre-emptive control of these compounds should be considered. In view of the numbers of compounds identified to date, there is also a future risk of misuse of new examples of 2-benzyl-benzimidazole opioids. This could also occur with piperidinyl benzimidazolone compounds, although the risk is likely to be lower as only buprenorphine has been detected from this group so far.
11. Clinical advice on management of toxicity with isotonitazene is already available for health professionals via TOXBASE, including recommendations on the use of naloxone as an antidote. However, specific information on buprenorphine and some other NSO considered in this report is not yet provided. Public Health England (now the Office for Health Improvements and Disparities) also issued a national patient safety alert regarding isotonitazene in August 2021. Drug treatment services are also aware of 2-benzyl benzimidazole opioids. It would be useful to make those who may use drugs better aware of these compounds and the risks they carry, especially users of heroin and

cocaine. Information on isotonitazene, brorphine and related compounds does not currently feature on the 'Frank' website ([www.talktofrank.com](http://www.talktofrank.com)) and this could usefully be updated to include these compounds in the synthetic opioids section.

12. The ACMD has considered two options for control, either listing specific 2-benzyl benzimidazole and piperidinyll benzimidazolone compounds known to have appeared anywhere in the world as NPS or generic controls intended to 'future-proof' the legislation by covering known and predicted variants which appear likely to present a significant risk to health.
13. Specifically listing currently identified variants for control is the simpler approach but risks being overtaken in the future by the development of further variants, as has been seen in other families of NPS. The NSO that have been identified in the UK or abroad at the time of preparing this report are as follows:
  - Metonitazene
  - Protonitazene
  - Isotonitazene
  - Butonitazene
  - Flunitazene
  - Metodesnitazene (metazene)
  - Etodesnitazene (etazene)
  - N-Pyrrolidino-etonitazene (etonitazepyne)
  - N-Piperidinyll-etonitazene (etonitazepipne)
  - Brorphine
14. Preparing generic controls is challenging, as these have to be designed so as to avoid inadvertently including materials of legitimate pharmaceutical interest which happen to include a 2-benzyl benzimidazole or piperidinyll benzimidazolone components within their chemical structure. The generic control developed in Germany (see Annex A) for 2-benzyl benzimidazoles provides a valuable model for these compounds and wording for a UK generic derived from this is presented below.
15. Currently the risk that 2-benzyl benzimidazole or piperidinyll benzimidazolone compounds other than those listed in paragraph 11.13 of the report may be misused in the UK is unknown. In the absence of a generic control these new compounds would not be

classified under the Misuse of Drugs Act, but examples with opioid activity would be captured by the Psychoactive Substances Act. The advice of the ACMD is therefore that legislation based on a generic chemical description should be developed, but introduction can await the following:

(a) the outcomes of work currently being done by the ACMD to reduce barriers to legitimate research with controlled drugs

(b) the outcome of a consultation with stakeholders, including academia and the chemical and pharmaceutical industries to ensure that any proposed legislation does not produce unintended barriers to research or legitimate commercial activity

In the meantime, monitoring should continue to detect any evidence of the misuse of new 2-benzyl benzimidazole or piperidiny benzimidazolone opioids.

The ACMD has made the following recommendations:

**Recommendation 1:** The following compounds 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).

- Metonitazene
- Protonitazene
- Isotonitazene
- Butonitazene
- Flunitazene
- Metodesnitazene (metazene)
- Etodesnitazene (etazene)
- N-Pyrrolidino-etonitazene (etonitazepyne)
- N-Piperidiny-etonitazene (etonitazepipne)
- Brorphine

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.

**Recommendation 2:** The following compounds should be deleted from schedule 2 and added to schedule 1 of the Misuse of Drugs Regulations 2001 (as amended).

- Etonitazene
- Clonitazene

Lead: Home Office

Measure of outcome: The inclusion of the listed compounds in schedule 1 of the Misuse of Drugs Regulations 2001.

**Recommendation 3:** The ACMD recommends that a consultation should be undertaken with stakeholders, including academia and the chemical and pharmaceutical industries on the introduction of a generic control on 2-benzyl benzimidazole variants, as new examples may be encountered and could present a serious risk of harm. Following this consultation, materials covered by the generic 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).

The proposed wording for the generic for addition to the Misuse of Drugs Act is as follows:

*Any compound (not being a compound for the time being specified in paragraph (a) above) structurally derived from 2-[(2-benzyl)-benzimidazol-1-yl]ethanamine by modification in any of the following ways, that is to say:*

- (i) By substitution at the nitrogen of the ethanamine to any extent by alkyl substituents containing up to three carbon atoms or alkenyl substituents containing up to three carbon atoms or by inclusion of the nitrogen atom (and no other atoms of the side chain) in a cyclic structure.*
- (ii) By substitution in the phenyl ring of the benzyl system to any extent by alkyl containing up to four carbon atoms, trifluoromethyl, alkoxy containing up to four carbon atoms, trifluoromethoxy, acetyloxy, hydroxy, cyano, thioalkyl containing up to four carbon atoms, alkylsulphonyl containing up to four carbon atoms or halogen substituents.*
- (iii) By substitution at the 5- or 6- positions of the benzimidazole system by nitro, acetyl, cyano, methoxy, trifluoromethyl or halogen substituents.*
- (iv) By substitution at the benzylic carbon by a methyl group*
- (v) By replacement of the benzylic carbon by a nitrogen, oxygen or sulphur atom*

*These modifications are subject to a maximum molecular mass of any derived compound of 500 atomic mass units.*

Note: Should evidence emerge of any variants of buporphine appearing, a

further generic control, requiring a similar consultation, should be considered.

Lead: Home Office

Measure of outcome: The inclusion of the described compounds in Class A of the Misuse of Drugs Act 1971 and schedule 1 of the Misuse of Drugs Regulations 2001, following appropriate consultation.

**Recommendation 4:** In light of the continuing emergence of NPS and particularly synthetic opioid NPS, a working group should be established to consider and provide recommendations on a UK-wide minimum standard set of post-mortem toxicology tests for apparent drug-related deaths, to include testing for relevant novel psychoactive substances to improve consistency of analysis and detection. The best practice recommendations agreed would include standards for reporting. This working group should include (but not necessarily be limited to) representation from the following:

- Chief Coroner's Office for England and Wales
- Coroners Service for Northern Ireland
- Crown Office and Procurator Fiscal Service Scotland
- UK and Ireland Association of Forensic Toxicologists
- London Toxicology Group
- Faculty of Forensic and Legal Medicine
- Office for Health Improvement and Disparities
- Home Office Forensic Early Warning System
- Police
- Local drug-related deaths review partnerships
- the ACMD

Lead: Home Office

Measure of outcome: A report detailing best practice for forensic sample analysis in the investigation of apparent drug-related deaths

**Recommendation 5:** Adequate funding should be made available by government to allow coroners, procurators fiscal and forensic toxicologists to follow the best practice guidelines developed via Recommendation 4.

Lead: Home Office

Measure of outcome: Consistent and appropriate forensic analysis and reporting for suspected drug-related deaths across the UK.



**Recommendation 6:** Information for health professionals (such as TOXBASE) and the general public (such as Frank) on the health effects of NSO should be reviewed and updated, ensuring that information is available in an appropriate format on NSO compounds including benzimidazole and piperidinyl benzimidazolone opioids and the risks that result from the inclusion of compounds of varying and sometimes very high potency in heroin preparations and counterfeit medicines.

Leads: National Poisons Information Service, UK Health Security Agency, Office for Health Improvement and Disparities

Measure of outcome: Information available for health professionals and the general public, including those with lived experience

We look forward to discussing the enclosed report with you in due course.

Yours sincerely,



Professor Owen Bowden-Jones

**Chair of ACMD**



Professor Simon Thomas

**Chair of ACMD NPS Committee**