ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Chris Philp MP
Minister for Crime, Policing and Fire
2 Marsham Street
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28 March 2024

Dear Minister,

Re: ACMD report – 'Recently encountered uncontrolled novel benzodiazepines and related compounds (2024 update)'

In recent years there has been increasing non-medical use of novel benzodiazepines. This has been associated with significant health harms, including an increase in annual numbers of deaths where a benzodiazepine has been implicated. The ACMD has previously provided advice on novel benzodiazepines, most recently in 2020, when 3 further compounds were recommended for control.

Since the publication of the previous report, the ACMD monitoring group has become aware of the detection and non-medical use of a further group of novel benzodiazepines in the UK and across Europe. Evidence was therefore sought from stakeholders concerning 18 different compounds detected in international markets to establish their prevalence in the UK.

The ACMD is pleased to enclose this report which considers the evidence of the harms and misuse of recently encountered uncontrolled novel benzodiazepines and related compounds and their prevalence in the UK. The report includes recommendations on the classification and scheduling of these substances.

Benzodiazepines are sedative and anxiolytic compounds with many licensed as medicines in the UK and internationally for the treatment of anxiety, insomnia, muscle spasms, spasticity or epilepsy. They are also associated

with important health harms including drowsiness, psychomotor impairment, unsteadiness, with high doses potentially causing loss of consciousness and respiratory depression, especially if used in combination with alcohol or other sedatives. Regular use may be associated with tolerance and dependence.

Based on the evidence obtained and reviewed on the uses and harms associated with these compounds, the ACMD has recommended that 15 of these substances should be controlled under the Misuse of Drugs Act 1971 (MDA) under Class C and Schedule I of the Misuse of Drugs Regulations 2001 (MDR).

The ACMD have drawn the following conclusions, options for control and recommendations from the evidence presented in this report:

Summary and Conclusions

1. A further 18 novel benzodiazepines or related compounds have appeared in international and UK drug markets since our last report on novel benzodiazepines in 2020.

2. Of these, **desalkylgidazepam, methylclonazepam** and **clobromazolam** have been detected by multiple sources in drug seizures, submitted drug samples and post mortem toxicology case work in the UK. There have also been occasional UK detections of **4'-Chloro-deschloroalprazolam** and **gidazepam.** These five compounds (or their active metabolites) have chemical structures similar to those of more established benzodiazepines and/or evidence of similar pharmacology. While the evidence of harms from these specific compounds is limited, it is very likely that these will be similar to those of more established benzodiazepines and therefore a similar level of control under the MDA as Class C compounds is appropriate.

3. There are also nine benzodiazepines or related compounds that have been detected in Europe, although not so far in the UK. These are **cloniprazepam, difludiazepam, thionordazepam, clobromazolam, fluclotizolam, deschloroclotizolam, flubrotizolam, fluetizolam and bentazepam**. These also present a potential risk of harm in the UK because of (a) direct evidence of harms associated with misuse and/or (b) their close structural similarity to currently controlled benzodiazepines that are known to be associated with harms.

4. A tenth compound, **rilmazafone**, although not a benzodiazepine, is converted to benzodiazepine metabolites in the body. Low doses are required for its clinical effects which are similar to those of currently controlled benzodiazepines. Rilmazafone has not yet been detected in

the UK, but it has been detected in Europe where it is reported to have caused at least one overdose death.

5. There is a significant risk of the 10 compounds listed in the two paragraphs above appearing in the UK, and of delays in their detection as the laboratory assays used may not look for them, one reason being lack of availability and affordability of appropriate chemical standards. To illustrate this, methylclonazepam and clobromazolam had been detected in Europe but not in the UK at the time of evidence collection for our previous report, but there have now been many detections of both of these compounds. In view of their potential harms, it is therefore also appropriate for these 10 substances to be classified as Class C compounds under the MDA 1971 now, rather than waiting for their detection in the UK before taking further action, based on their potential harms.

6. For the remaining 3 compounds considered in this report, the ACMD considers that there is currently inadequate evidence of harms or potential harms. Therefore, they do not require control via the MDA of 1971 unless further evidence of harms appears in the future:

   Cinazepam has complex pharmacology, being a partial agonist but with a major metabolite that is a full agonist. The result is relatively weak sedative and muscle relaxant effects. Although detected in Europe in 2019, Cinazepam has not yet been detected in the UK. As a medicinal product, it is exempted from the PSA (2016).

   Tofisopam is a 2,3-benzodiazepine that does not act on the GABA receptor, and in comparison to most 1,4 benzodiazepines, is of lower potency and higher recommended medicinal dosage (300 mg/day). There has been only a single detection of tofisopam in the UK. It is also exempted from the PSA (2016) because it meets the definition of a medicinal product.

   Alprazolam triazolobenzophenone is not a benzodiazepine but is converted to the Class C compound alprazolam in the body. Although first detected in Europe in 2014, it has rarely been encountered since and never in the UK.

7. It should be noted that the previous lack of appropriate standards for gidazepam, rilmazafone and alprazolam triazolobenzophenone may have resulted in their involvement in fatal cases of toxicity not being recognised. It is less likely that these compounds would not be identified correctly in seized drug samples as if necessary these

samples will be sent on for more complex analysis in specialist laboratories using techniques like Nuclear Magnetic Resonance (NMR) and/or high-resolution mass spectrometry (HRMS).

8. All but two of the 15 compounds recommended for control under the MDA 1971 are not currently licensed as medicines in any country in the world. These 13 unlicensed compounds should therefore be placed in Schedule 1 of the MDR. They should also be designated as controlled drugs to which section 7(4) of the MDA 1971 applies, since they have no recognised medicinal use outside of research in the UK.

9. Gidazepam and rilmazafone (#17) are licensed as medicines in other countries but not in the UK. Of particular importance, gidazepam is licensed in Ukraine and there are currently substantial numbers of Ukrainian refugees in the UK. It is important that scheduling decisions affecting these compounds do not create a barrier to legitimate prescribing for those already stabilised on these medicines that is disproportionate to their risks of misuse.

10. The ACMD, however, has not received any evidence of the licensed importing or prescribing of gidazepam or rilmazafone on a named patient basis to patients in the UK. The ACMD therefore advises that these compounds should also be placed in Schedule 1 of the MDR, consistent with the ACMD Standard Operating Procedure [ACMD 2021] and be designated as controlled drugs to which section 7(4) of the MDA 1971 applies.

11. If there are people in the UK who need prescriptions of these compounds, personal licenses can be granted to allow import of Schedule 1 drugs in exceptional circumstances [Home Office, 2019], although this could be challenging for patients and healthcare professionals to negotiate and might compromise ongoing treatment. A license is also required should visitors need to bring medicines into the UK that are listed in Schedule 1.

12. Should evidence emerge of significant legitimate importing or prescribing on a named patient basis of gidazepam or rilmazafone, the Government may consider one or both of the following actions:

    (a) Commissioning guidance for healthcare professionals on how to safely transfer patients from these drugs to a suitable alternative that is licensed in the UK.

    (b) Placing them in Schedule 4 Part 1 of the MDR (consistent with most benzodiazepines that are licensed in the UK). Under these

circumstances they should not be designated as controlled drugs to which section 7(4) of the MDA 1971 applies.

Recommendations

Recommendation 1: The ACMD recommends that the following 15 substances are classified under Class C of the Misuse of Drugs Act 1971, consistent other classified benzodiazepines.

- Gidazepam
- Desalkylgidazepam
- Methylclonazepam
- Cloniprazepam
- Difludiazepam
- Thionordazepam
- Clobromazolam
- 4'-Chloro-deschloroalprazolam
- Fluclotizolam
- Deschloroclotizolam
- Flubrotizolam
- Fluetizolam
- Bentazepam
- Bretazenil,
- Rilmazafone

Leads: Home Office

Measure of outcome: The inclusion of these compounds in Class C of the Misuse of Drugs Act 1971.

Recommendation 2: The ACMD recommends that the following should be added to Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) because they have no medicinal use in the UK. They should also be designated as controlled drugs to which section 7(4) of the 1971 Act applies.

- Gidazepam
- Desalkylgidazepam
- Methylclonazepam
- Cloniprazepam
- Difludiazepam

- Thionordazepam
- Clobromazolam
- 4'-Chloro-deschloroalprazolam
- Fluclotizolam
- Deschloroclotizolam
- Flubrotizolam
- Fluetizolam
- Bentazepam
- Bretazenil,
- Rilmazafone

Leads: Home Office

Measure of outcome: The inclusion of these compounds in Schedule 1 of the Misuse of Drugs Regulations 2001 and designation as controlled drugs to which section 7(4) of the 1971 Act applies.

We welcome the opportunity to discuss this report in due course.

Yours sincerely,

Professor Owen Bowden-Jones
Chair of ACMD

Professor Simon Thomas
Chair of NPS Committee