ACMD

Advisory Council on the Misuse of Drugs

ACMD Chair: Prof Owen Bowden-Jones
Diphenidine Working Group Secretaries: Yetunde Animashawun & Ana Ali
1st Floor (NE), Peel Building
2 Marsham Street
London
SW1P 4DF
ACMD@homeoffice.gov.uk

Rt Hon Suella Braverman KC MP
Home Secretary
2 Marsham Street
London, SW1P 4DF

25 May 2023

Dear Home Secretary,

Re: ACMD Report – Review of the Evidence on the Use and Harms of Diphenidine and Related Substances.

In January 2022, the then-Home Secretary commissioned the Advisory Council on the Misuse of Drugs (ACMD) for advice on the appropriate classification under the Misuse of Drugs Act 1971 and scheduling under the Misuse of Drug Regulations 2001 of the 1,2-diarylethylamine, diphenidine. The Home Office was obliged to undertake this when diphenidine was added to Schedule II of the Convention on Psychotropic Substances of 1971 during the 64th Commission on Narcotic Drugs (CND) meeting in April 2021.

The ACMD is pleased to enclose the attached report, describing the use and harms of diphenidine and related substances ephenidine, methoxyphenidine, fluorolintane and isophenidine. The report provides recommendations on their classification and scheduling, following a thorough review of the evidence available and utilising the expertise of the ACMD Diphenidine Working Group members.

Diphenidine, methoxyphenidine and ephenidine have similar pharmacological action and toxicity to ketamine and are recommended to be controlled comparably. As these compounds have the potential to cause harm, pose a threat to the public and have no known legitimate uses, the ACMD has recommended that they should be controlled under the Misuse of Drugs Act 1971 under Class B. There is limited evidence for the related substances fluorolintane and isophenidine to recommend that they be controlled at this time and should thus remain subject to the controls of the Psychoactive Substances Act 2016.

The ACMD have drawn the following conclusions and proposed recommendations from the evidence presented in this report:

Conclusions:

1. Diphenidine is a 1,2-diarylethylamine and has been reported to have dissociative effects as a derivative of lefetamine, a stimulant controlled as a Class B substance under the UK's Misuse of Drugs Act 1971. Other related variants included methoxyphenidine (also referred to as methoxphenidine), fluorolintane, isophenidine and ephenidine.

2. In October 2020, the 43rd meeting of the World Health Organization Expert Committee on Drug Dependence reviewed the 1,2-diarylethylamines diphenidine and methoxyphenidine. Based on the recommendations of these reviews, the 64th Commission on Narcotic Drugs (CND) meeting in April 2021 voted to add diphenidine to the UN Convention on Psychotropic Substances 1971 as a Schedule II material. The CND meeting decided that methoxyphenidine would not be added to the UN Convention on Psychotropic Substances 1971 at this time, but would remain under continuing UN surveillance. The other related substances, fluorolintane, ephenidine and isophenidine have not as yet been reviewed by the WHO.

3. Although there was an EU patent approved in 1989 for the potential use of 1,2-diarylethylamines in the treatment of neurotoxic injury, outside of synthesis for research or analytical purposes, there are no approved medicinal, veterinary or industrial use for diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine.

4. Diphenidine and related compounds all act as relatively potent antagonists of the NMDA receptor, a cell protein found throughout the brain that mediates neuronal (brain cell) activation. Based on the available pharmacological data, diphenidine and related compounds are highly potent inhibitors of NMDA receptor function, making them more similar to ketamine than memantine. There is no evidence to suggest that diphenidine, methoxyphenidine and ephenidine cause the bladder-related issues which can occur with chronic ketamine use.

5. There are no population or sub-population data on the prevalence of use of diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine and there are no published cases or detections in acute toxicity cases of ephenidine, fluorolintane or isophenidine. The use of diphenidine and methoxyphenidine appears to be low based on the small number of cases of acute toxicity and deaths. Additionally, the reports and deaths are historical with none occurring in the UK or elsewhere since 2019.

6. The information from the case reports/series, Euro-DEN Plus cases and the IONA detection cases have shown that the clinical features seen were of acute stimulant (e.g. hypertension and tachycardia) and neuropsychiatric (hallucinations, sedation/drowsiness, confusion, paranoia and anxiety/agitation) toxicity. These features are similar to drugs such as ketamine. It should be noted that in the majority of self-reported use or analytically detected cases there were

other substances detected that could have explained some or all of the reported clinical features seen.

7. As diphenidine has been controlled under the UN Convention on Psychotropic Substances 1971 as a Schedule II material, it has to be controlled under the UK's Misuse of Drugs Act 1971. There is evidence that diphenidine, methoxyphenidine and ephenidine have similarities to ketamine from pharmacological studies and/or cases of acute toxicity and, therefore, the control of these substances should be similar to that for ketamine. There is limited or no evidence for the related substances fluorolintane and isophenidine to recommend that they be controlled at this time. They should remain subject to the controls of the Psychoactive Substances Act 2016 and under active monitoring by the Advisory Council of the Misuse of Drugs (ACMD). If any evidence of their use and related harm subsequently becomes available, further consideration at that time for control under the Misuse of Drugs Act 1971 would be appropriate.

Recommendation:

1. The following compounds *(listed under point 2 underneath)* should be added to Class B of the Misuse of Drugs Act 1971, consistent with the classification of ketamine and other controlled dissociatives such as methoxetamine and PCP-related materials.

2. 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 added to Schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015, to which section 7(4) of the Misuse of Drugs Act 1971 applies.

    - Diphenidine
    - Ephenidine
    - Methoxyphenidine (also known as methoxphenidine)

Lead: Home Office

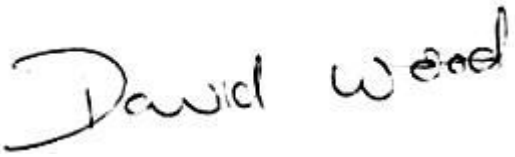
Measure of outcome: The inclusion of the listed compounds in Class B of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001 and the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015.

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

Yours sincerely,

Professor Owen Bowden-Jones

Chair of the ACMD



Dr David Wood

Diphenidine and related substances Working Group Chair