Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

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2-METHYL AP-237
(Street Name: 2-MAP)

Introduction:

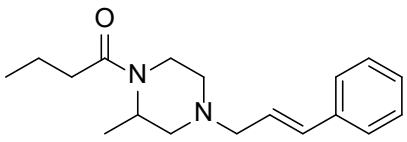
2-Methyl AP-237 is a novel synthetic drug with opioid agonist-like activity. Beginning in 2019, 2-methyl AP-237 emerged on the illicit synthetic drug market, as evidenced by its identification in drug seizures. Abuse of 2-methyl AP-237, similar to that of other synthetic opioids, has been associated with adverse health effects, including death. Adverse health effects associated with the abuse of synthetic opioids, as well as their continued evolution, increased popularity, and increased availability of these substances, have been a serious concern in recent years and pose an imminent hazard to public safety. As the United States continues to experience an unprecedented epidemic of opioid misuse and abuse, the presence of new synthetic opioids with no approved medical use exacerbates the epidemic.

Licit Uses:

2-Methyl AP-237 is not approved for medical use in the United States.

Chemistry:

2-Methyl AP-237 is chemically known as 1-(2-methyl-4-(3-phenylprop-2-en-1-yl)piperazin-1-yl)butan-1-one (CAS 98608-61-8; hydrochloride salt 98608-59-4). 2-Methyl AP-237 is a methyl analogue of the opioid analgesic bucinnazine, which is also known as AP-237. Chemical syntheses of 2-methyl AP-237 and other piperizino derivatives—such as AP-237, para-methyl AP-237, and AP-238—were originally patented in the 1980s. The chemical structure of 2-methyl AP-237 is shown below:



Pharmacology:

Data obtained from pre-clinical studies demonstrate that 2-methyl AP-237 exhibits mu-opioid receptor agonist pharmacological properties. According to the patent, an *in vivo* (in mice) study indicated that at higher doses, 2-methyl AP-237 produced analgesic effects in a hot plate assay. In an *in vivo* drug discrimination study conducted in rats, results indicated that 2-methyl AP-237 fully substitutes for the discriminative stimulus effects of morphine and is approximately 4 times more potent than morphine. Data from *in vitro* studies showed that 2-methyl AP-237, similar to fentanyl and morphine, binds to the mu-opioid receptors. Additionally, in an *in vitro* functional assay, 2-methyl AP-237 activated mu-opioid receptors, albeit at a lower percentage of maximum stimulation when compared to fentanyl and morphine. These data demonstrate that 2-methyl AP-237 has mu-opioid receptor agonist-like activity. It is well established that substances that act as mu-opioid receptor agonists have a high potential for addiction and can cause dose-dependent respiratory depression. In fact, abuse of 2-methyl AP-237 has been associated with at least five fatalities and two nonfatal overdoses in the United States.

Illicit Uses:

2-Methyl AP-237 is abused for its opioidergic effects.

User Population:

The population likely to abuse 2-methyl AP-237 appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, depressants, fentanyl, and other synthetic opioid substances. This is evidenced by the types of drugs co-identified with 2-methyl AP-237 in associated fatal and nonfatal overdose cases. Because abusers of 2-methyl AP-237 are likely to obtain this substance through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent. Due to this, 2-methyl AP-237 poses significant adverse health and safety risks for end users. Thus, the positive identification of this substance in numerous overdoses and at least ten postmortem cases is of concern to the public safety.

Illicit Distribution:

Law enforcement data indicate that 2-methyl AP-237 has appeared in the U.S. illicit drug market. Law enforcement has encountered 2-methyl AP-237 as an encapsulated powder.

The Drug Enforcement Administration's National Forensic Laboratory Information System (NFLIS) Drug database collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories. NFLIS-Drug received 21 reports of 2-methyl AP-237 in 2019, 5 in 2020, 49 in 2021, 15 in 2022, 11 in 2023, and 13 in 2024 (reports still pending). These reports included identification of 2-methyl AP-237 alone and in combination with other substances.

The lack of approved medical use and the presence of at least ten known overdose deaths associated with the abuse of 2-methyl AP-237 underscore the potential public health threat posed by its presence in the illicit drug market.

Control Status:

2-Methyl AP-237 is controlled in schedule I of the Controlled Substances Act.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or E-mail DPE@dea.gov.