

## ISOTONITAZENE

### Introduction:

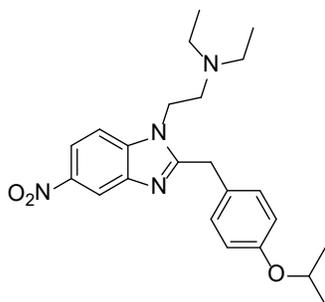
Isotonitazene is a potent synthetic opioid, and it is being abused for its opioidergic effects. The abuse of isotonitazene, similar to other synthetic opioids, has been associated with adverse health effects, including numerous deaths. The availability of synthetic opioids in the illicit drug market continues to pose an imminent hazard to the public safety. Adverse health effects associated with the abuse of synthetic opioids and the continued evolution and increased popularity of these substances have been a serious concern in recent years. 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. Beginning in April 2019, isotonitazene emerged on the illicit synthetic drug market as evidenced by its identification in drug seizures.

### Licit Uses:

Isotonitazene is not approved for medical use in the United States.

### Chemistry:

Isotonitazene is chemically known as, *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine. Chemical syntheses of isotonitazene and other schedule I synthetic opioid substances containing a benzimidazole core, such as etonitazene and clonitazene, were first reported in the late 1950s. The chemical structure of isotonitazene is shown below:



### Pharmacology:

Data obtained from pre-clinical studies demonstrate that isotonitazene exhibits a pharmacological profile similar to that of etonitazene and other mu-opioid receptor agonists. In an *in vivo* (in mice) study, isotonitazene was more potent than morphine as an analgesic in a tail-flick assay. Data from *in vitro* studies showed that isotonitazene, similar to fentanyl and hydromorphone, activates the mu-opioid receptors. Activation of the mu-opioid receptors by isotonitazene has been reported to involve recruitment of  $\beta$ -arrestin-2, a regulatory protein. Studies have shown that mu-opioid receptor and  $\beta$ -arrestin-2 interaction is implicated in some of the adverse effects of opioid analgesics. Naloxone, an opioid receptor antagonist, blocked isotonitazene's activation of the

mu-opioid receptor. These data demonstrate that isotonitazene, similar to fentanyl and other mu-opioid receptor agonists, binds to, and activates the mu-opioid receptor.

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, the abuse of isotonitazene has been associated with fatalities in the United States.

### Illicit Uses:

Isotonitazene is abused for its opioidergic effects.

### User Population:

The population likely to abuse isotonitazene appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, fentanyl, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in isotonitazene seizures and in fatal overdose cases. Abusers of isotonitazene are likely to obtain this substance through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user. Consistent with other mu-opioid receptor agonists, the potential health and safety risks for users of isotonitazene are high. The positive identification of this substance in overdose and post-mortem cases is a serious concern to the public safety.

### Illicit Distribution:

Law enforcement data indicate that isotonitazene has appeared in the United States illicit drug market. Law enforcement has encountered isotonitazene primarily in powder form. In April 2019, the United States Customs and Border Protection seized 1.6 grams of isotonitazene in California.

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 has received 900 reports of isotonitazene alone or in combination with other substances. With no approved medical use, numerous overdose deaths associated with the abuse of isotonitazene underscore the public health threat posed by its presence in the illicit drug market.

### Control Status:

Isotonitazene is a schedule I substance under the Controlled Substances Act.