

## FENTANYL

(Trade Names: Actiq<sup>®</sup>, Fentora<sup>™</sup>, Abstral<sup>®</sup>, Subsys<sup>™</sup>, Lazanda<sup>®</sup>, Duragesic<sup>®</sup>)

### Introduction:

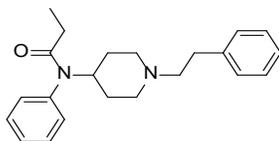
Fentanyl is a potent synthetic opioid. It was introduced into medical practice as an intravenous anesthetic under the trade name of Sublimaze<sup>®</sup> in the 1960s.

### Licit Uses:

According to the IQVIA National Prescription Audit<sup>™</sup>, total prescriptions dispensed for fentanyl were approximately 6.5 million in 2015, 5.0 million in 2017, 3.2 million in 2019, 2.4 million in 2021, and 1.9 million in 2023. Fentanyl pharmaceutical products are currently available as oral transmucosal lozenges, commonly referred to as fentanyl “lollipops” (Actiq), effervescent buccal tablets (Fentora), sublingual tablets (Abstral), sublingual sprays (Subsys), nasal sprays (Lazanda), transdermal patches (Duragesic), and injectable formulations. Oral transmucosal lozenges and effervescent buccal tablets are used for the management of breakthrough cancer pain in patients who are already receiving opioid medication for their underlying persistent pain. Transdermal patches are used in the management of chronic pain in patients who require continuous opioid analgesia. Fentanyl citrate injections are administered intravenously, intramuscularly, spinally, or epidurally for potent analgesia and anesthesia. Due to a concern about deaths and overdoses resulting from fentanyl transdermal patches (Duragesic and generic versions), on July 15, 2005, the Food and Drug Administration issued safety warnings and reiterated the importance of strict adherence to the guidelines for the proper use of these products.

### Chemistry:

Fentanyl is chemically known as *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide. Fentanyl is a solid that exists in a crystal or crystalline powder form. The chemical structure of fentanyl is shown below:



### Pharmacology:

Fentanyl is about 100 times more potent than morphine as an analgesic. It is a  $\mu$ -opioid receptor (MOR) agonist with high lipid solubility and a rapid onset and short duration of effects. Fentanyl rapidly crosses the blood-brain barrier. It is similar to other MOR agonists (like morphine or oxycodone) in its pharmacological effects and produces analgesia, sedation, nausea, vomiting, itching, and respiratory depression. Fentanyl appears to produce muscle rigidity with greater frequency than other opioids. Unlike some MOR agonists, fentanyl does not cause histamine release and has minimal depressant effects on the heart.

### Illicit Uses:

Fentanyl is abused for its intense euphoric effects. Fentanyl can serve as a direct substitute for heroin in opioid dependent individuals. However, fentanyl is a very dangerous substitute for heroin, because fentanyl is much more potent than heroin and results in frequent overdoses that can lead to respiratory depression and death.

Fentanyl patches are abused by removing the gel contents from the patches and then injecting or ingesting these contents. Patches have also been frozen, cut into pieces, and placed under the tongue or in the cheek cavity for drug absorption through the oral mucosa. Used patches are attractive to abusers as a large percentage of fentanyl remains in these patches even after a 3-day use. Fentanyl oral transmucosal lozenges and injectables are also diverted and abused.

Abuse of fentanyl initially appeared in mid-1970s and has increased in recent years. There have been reports of deaths associated with abuse of fentanyl products. According to the Centers for Disease Control and Prevention (CDC), in 2022, more than 73,000 drug overdose deaths involving synthetic opioids (other than methadone) occurred in the United States, which was more deaths than from any other drug class. This was 68 percent of all drug overdose deaths (107,941 total). Synthetic opioid-involved overdose death rates increased by over 30% from 2020 to 2022 and accounted for 75% of all opioid-involved deaths in 2022. For comparison, the number of overdose deaths involving synthetic opioids (excluding methadone) was 3,105 in 2013. While the synthetic opioid category does include other substances such as tramadol, fentanyl largely dominates the category.

According to the Drug Enforcement Administration’s (DEA) National Drug Threat Assessment, illicitly manufactured fentanyl (IMF) by the Mexican cartels is the main driver of the ongoing opioid epidemic in the United States. DEA continues to seize significant amount of IMF every year, from 6,875 kg in 2021 to 13,176 kg in 2023. Fake prescription pills containing fentanyl is of serious concern and poses significant threat to public safety. In 2023, DEA forensic laboratory analysis showed that about 7 in 10 fake pills contain a potentially lethal dose of fentanyl.

### Illicit Distribution:

Licit fentanyl is diverted via theft, fraudulent prescriptions, and illicit distribution by patients, physicians, and pharmacists.

DEA’s National Forensic Laboratory Information System (NFLIS) Drug database collects scientifically verified data on drug items and cases submitted to and analyzed by federal, state, and local forensic drug laboratories. NFLIS-Drug, however, does not distinguish between pharmaceutical and illicitly manufactured fentanyl. NFLIS-Drug received more than 126,000 reports of fentanyl in 2020, which continued to increase annually to more than 166,000 in 2021; more than 173,000 in 2022; and approximately 168,000 for 2023.

### Clandestine Manufacture:

From April 2005 to March 2007, an outbreak of fentanyl overdoses and deaths occurred. CDC and DEA’s surveillance system reported 1,013 confirmed non-pharmaceutical fentanyl-related deaths. Most of these deaths occurred in Delaware, Illinois, Maryland, Michigan, Missouri, New Jersey, and Pennsylvania. Consequently, DEA immediately undertook the development of regulations to control precursor chemicals used by clandestine laboratories to illicitly manufacture fentanyl. In 2007, DEA published an Interim Final Rule to designate *N*-phenethyl-4-piperidone (NPP)—a precursor to fentanyl, as a list I chemical. DEA also completed a scheduling action to designate 4-anilino-*N*-phenethylpiperidine (ANPP) as a schedule II immediate precursor in 2010. In an effort to address the continued evolution of precursors used in the illicit manufacture of fentanyl, DEA completed regulations to add benzylfentanyl and 4-anilinopiperidine (4-AP) as list I chemicals and to control norfentanyl as a schedule II immediate precursor to fentanyl. DEA has since expanded the definition of 4-AP to include amides, carbamates, and halides. In 2023, DEA added 4-piperidone as a list I chemical.

### Control Status:

Fentanyl is controlled in schedule II 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 Email [DPE@dea.gov](mailto:DPE@dea.gov).