Fentanyl
(Trade Names: Actiq®, Fentora™, Duragesic®)

Introduction:
Fentanyl is a potent synthetic opioid. It was introduced into medical practice as an intravenous analgesic under the trade name of Sublimaze in the 1960s.

Licit Uses:
According to IQVIA National Prescription Audit™, total prescriptions dispensed for fentanyl were approximately 6.5 million in 2015, 5.0 million in 2017, 3.2 million in 2019, 2.7 million in 2020, and 2.4 million in 2021. During the height of the opioid epidemic, in 2016 and 2017, the number of fentanyl prescriptions dispensed were approximately 6.0 million and 5.0 million, respectively. 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, intranasally, or epidurally for potent analgesia and anesthesia. Because of 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 ([N-phenyl-N-[1-(2-phenylethyl)-4-piperidiny]propanamide] is a water-soluble solid that exists in a crystalline powder form.

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Pharmacology:
Fentanyl is about 100 times more potent than morphine as an analgesic. It is a μ-opioid receptor 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 μ-opioid receptor 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 μ-opioid receptor 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 it 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 fentanyl injectables are also diverted and abused.

Abuse of fentanyl 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 2020, more than 56,000 deaths involving synthetic opioids (other than methadone) occurred in the United States, which is more deaths than from any other drug class. Synthetic opioid-involved death rates increased by over 56% from 2019 to 2020 and accounted for over 82% of all opioid-involved deaths in 2020. The rate of overdose deaths involving synthetic opioids was more than 18 times higher in 2020 than in 2013. While the synthetic opioid category does include other substances such as tramadol, fentanyl largely dominates the category. Also, as annually reported by the DEA National Drug Threat Assessment, in March 2021, states with the greatest amounts of fentanyl seized in 2019 were either clustered along the Southwest border, or were located in the Mid-Atlantic, Great Lakes, or Northeast areas of the United States.

Illicit Distribution:
Licit fentanyl is diverted via theft, fraudulent prescriptions, and illicit distribution by patients, physicians, and pharmacists. Illicitly manufactured fentanyl is chiefly responsible for the current domestic crisis. According to the National Forensic Laboratory Information System (NFLIS) database, which does not distinguish between pharmaceutical and illicitly manufactured fentanyl, the annual number of fentanyl reports in 2017 was 61,628 and 89,894 in 2018, which were analyzed by federal, state and local forensic laboratories in the United States. Fentanyl reports continued to rise in 2019 with 107,966 reports, and again in 2020 with 125,119 reports. In 2021, 159,645 fentanyl drug reports were submitted to NFLIS. Preliminary findings indicate a greater increase with 86,414 reports of fentanyl identified in 2018.

Clandestine Manufacture:
From April 2005 to March 2007, an outbreak of fentanyl overdoses and deaths occurred. The Centers for Disease Control and Prevention (CDC)/Drug Enforcement Administration (DEA) 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. After the control of ANPP, the number of fentanyl-related deaths declined until 2013. In effort to address the continued evolution of precursors used in the illicit manufacture of fentanyl, DEA recently 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.

Control Status:
Fentanyl is controlled in schedule II of the Controlled Substances Act.