



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

September 2019

Introduction:

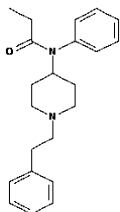
Fentanyl is a potent synthetic opioid. It was introduced into medical practice as an intravenous anesthetic under the trade name of Sublimaze in the 1960s.

Licit Uses:

In 2015, there were 6.5 million fentanyl prescriptions dispensed in the U.S. And, during the height of the opioid epidemic, in 2016 and 2017, the number of fentanyl prescriptions dispensed decreased to 5.96 million and 5.05 million, respectively; with, 4.0 million prescriptions sold in 2018 (IQVIA™ previously known as IMS Health™). Fentanyl pharmaceutical products are currently available as oral transmucosal lozenges, commonly referred to as the fentanyl “lollipops” (Actiq®), effervescent buccal tablets (Fentora™), sublingual tablet (Abstral®), sublingual spray (Subsys™), nasal spray (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. 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*-(1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide) is a water-soluble solid substance that exists in a crystal or crystalline powder form.



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 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) a 73 percent increase in synthetic opioid deaths occurred in the U.S., from 5,544 in 2014 to 9,580 in 2015. In 2016, the nationwide synthetic opioid death toll rose to 103 percent with 19,413 recorded fatalities, as well as, a 47 percent increase with 28,466 deaths in 2017. 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 October 2017, and recent CDC journal literature, there is a strong correlation between the number of synthetic opioid deaths and the number of fentanyl exhibits encountered by forensic laboratories; demonstrating when the number of fentanyl exhibits in NFLIS increase, so does the number of synthetic opioid deaths recorded by the CDC.

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), which does not distinguish between pharmaceutical and illicitly manufactured fentanyl, there were 5,539 reports/exhibits of fentanyl for 2014 and 15,458 in 2015 (a 179.1 percent increase) by federal, state and local forensic laboratories in the United States. During the peak of the opioid epidemic, fentanyl reports/exhibits more than doubled to 37,314 in 2016 (a 141 percent increase from 2015) and 61,714 reports/exhibits in 2017. Preliminary findings indicate a greater increase with 86,414 reports/exhibits 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 the precursor chemicals used by the 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 1 chemical. DEA also completed a scheduling action of designating another chemical precursor, 4-anilino-*N*-phenethyl-4-piperidine (ANPP) as a schedule II immediate precursor in 2010. After the control of ANPP, the number of fentanyl-related deaths declined until 2013.

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@usdoj.gov.