



METHADONE

(Trade Names: Methadose®, Dolophine®; Street Names: Fizzies, Amidone, Chocolate Chip Cookies)

December 2019

Introduction:

Methadone, a pharmaceutical opioid, is currently marketed as oral concentrate (10 mg/ml), oral solution (5 and 10 mg/5ml), tablet (5, 10, and 40 mg), injection (10mg/ml) and powder (50, 100, and 500 mg/bottle for prescription compounding).

According to the National Center for Health Statistics (NCHS) Health E-Stats publication, poisoning deaths increased 66% from 19,741 in 1999 to 32,691 in 2005. During the same time period, methadone deaths increased 469% to 4,460 (14% of all poisonings); however, recently, with the exception of subpopulations, U.S. methadone overdose deaths have decreased by 24% to 3,373 in 2016; and, have continued to steadily decrease in 2017 and 2018 for U.S. population, in general. In November 2006, the Food and Drug Administration (FDA) issued a public health advisory stating that methadone use in pain control may result in life-threatening cardiac and respiratory changes and deaths. FDA further advised that methadone doses for pain relief should be carefully selected, slowly titrated and carefully monitored by the prescribing physician. As of January 1, 2008, manufacturers of 40 mg methadone hydrochloride dispersible tablets have voluntarily agreed to restrict distribution of this formulation to only hospitals and those facilities authorized for detoxification and maintenance treatment of opioid addiction. The 40 mg methadone product is not FDA approved for use in the management of pain.

Licit Uses:

Methadone has been used for over forty years primarily as a detoxification and maintenance treatment of opioid addiction. In recent years, methadone is also being increasingly prescribed for relief of moderate to severe pain. The number of prescriptions dispensed and/or sold for methadone products in the U.S. continued to decrease from 2.9 million in 2016 to 2.6 million in 2017; and, 2.2 million in 2018. (IQVIA™). Methadone products, when used for treatment of narcotic addiction in detoxification or maintenance programs, shall be dispensed only by pharmacies approved by appropriate regulatory authorities. When used as analgesics, they may be dispensed by any licensed pharmacy.

Chemistry/Pharmacology:

Methadone, (RS)-6-(dimethylamino)-4,4-diphenylheptan-3-one, is a synthetic drug with *mu*-opioid receptor agonist activity. Pharmacological and toxic effects, abuse and dependence liabilities of methadone are qualitatively similar to those of other schedule II opioid analgesics such as morphine and oxycodone. Analgesic activity of racemic methadone is entirely due to its *l*-isomer, 8 to 50 times more potent than *d*-isomer. The *d*-isomer lacks significant respiratory depressant action and addiction liability, but possesses antitussive activity. The analgesic effect of 8 to 10 mg of methadone is almost

equivalent to that of 10 mg of morphine. With respect to total analgesic effects, methadone given orally is one-half as effective as its intramuscular administration. Pain relief from a dose of methadone lasts about 4 to 8 hours, but the drug may stay in the body for 8 to 59 hours.

Methadone binds strongly to proteins in various tissues, including the brain. Upon discontinuation of its administration, low concentrations of methadone are maintained in the body because of the slow release of methadone from tissue binding sites. Notable features of methadone are its efficacy by the oral route, its prolonged duration of action in suppressing withdrawal symptoms in physically dependent individuals and its tendency to produce persistent effects with repeated administration. Acute overdose of methadone, similar to morphine, can produce severe respiratory depression, somnolence, coma, skeletal muscle flaccidity, cool clammy skin, constricted pupils, reduction in blood pressure and heart rate, pulmonary edema and death. Pure opioid antagonists such as naloxone are specific antidotes against respiratory depression from methadone overdose.

Illicit Uses:

Methadone has abuse potential and may produce psychic and physiologic dependence and tolerance. According to the National Survey on Drug Use and Health (NSDUH), 346,000 persons aged 12 and older in 2016 reported that they had misused methadone in the past year, a decrease from 502,000 persons in 2015. For 2017 and 2018, the decrease continued with 261,000 and 256,000 persons, aged 12 and older, respectively, who indicated past year misuse of methadone. The American Association for Poison Control Centers (AAPCC) reported 2,906 case mentions (1,217 single exposures) and 8 deaths associated with methadone in 2016, and 2,611 case mentions (1,054 single substance exposures), and 16 deaths in 2017.

Illicit distribution:

According to the National Forensic Laboratory Information System (NFLIS) and the System to Retrieve Information from Drug Evidence (STRIDE)/STARLiMS, 4,142 methadone drug reports were identified by federal, state, and local forensic laboratories in 2016, 3,195 in 2017, and approximately 2,425 in 2018.

Control status:

Methadone is in schedule II of the Controlled Substances Act (CSA).

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.