FURANYL FENTANYL

Critical Review Report

Agenda Item 4.6

Expert Committee on Drug Dependence

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World Health Organization

Contents

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Summary

Furanyl Fentanyl is a new designer opioid drug. It is a derivative of fentanyl with two distinctive characteristics:

1) higher liposolubility that allows its rapid absorption into general circulation
2) It binds to μ-opioid receptors with significant higher affinity than morphine.

These characteristics give furanyl fentanyl a highly risky pharmacological profile.

In the last several years there has been an increase in deaths due to the use of this designer opioid. Furthermore, it has been reported that it might be present in cocaine crack and other illicit drugs sold on the black market.

1. Substance identification

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

101345-66-8 furanyl fentanyl base
101365-56-4 furanyl fentanyl hydrochloride

C. Other Chemical Names

N-(1-phenethylpiperidin-4-yl)-*N*-phenylfuran-2-carboxamide
N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide
N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide
2-furanoylfentanyl,
FU-F,
Fu-F,
UNII-3F7C9J1LS7
3F7C9J1LS7
UNII-3F7C9J1LS7
3F7C9J1LS7
Furanylfentanyl
Furanyl fentanyl
Fu-F
DEA No. 9834
SCHEMBL10847816
ZINC34114397
AKOS025395472
101345-66-8

D. Trade Names

None

E. Street Names

China white

F. Physical Appearance

White powder

G. WHO Review History

Furanyl fentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that furanyl fentanyl is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.

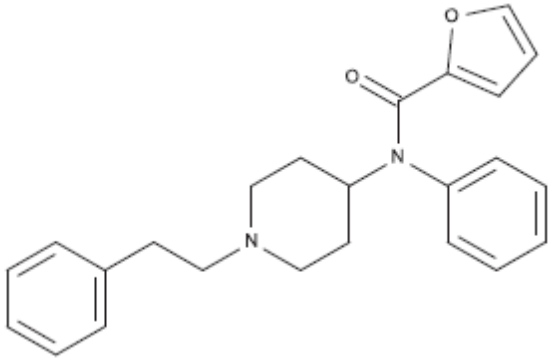
2. Chemistry

A. Chemical Name

IUPAC Name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide
CA Index Name: N/A

B. Chemical Structure

Free base:



Molecular Formula: C24H26N2O2
Molecular Weight: 374.484 g/mol

C. Stereoisomers

None

D. Methods and Ease of Illicit Manufacturing

The synthesis of furanyl fentanyl was first described in a 1986 patent (Huang et al., 1986). According to the EMCDDA-Europol Joint Report (2017), the methods developed for the synthesis of fentanyl are applicable to the synthesis of furanyl fentanyl as it relies on similar precursors and synthetic methods. Furanyl fentanyl can also be produced through the addition of 2-furoyl chloride to the precursor 4-ANPP.

E. Chemical Properties

Melting point: unknown
Boiling point: unknown
Solubility: Furanyl fentanyl is highly lipophilic, thus it has very low solubility in water.

F. Identification and Analysis

Liquid chromatography–tandem mass spectrometry (LC-MS/MS) has been used to analytically confirm furanyl fentanyl in post-mortem blood samples (Mohr et al., 2016; Sofalvi et al., 2017)

EMCDDA-Europol Joint Report (2017) states that gas chromatography – mass spectrometry (GC-MS), high performance liquid chromatography time-of-flight (HPLC-TOF), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR) and nuclear magnetic resonance (NMR) techniques can also be used to analytically confirm furanyl fentanyl.

3. Ease of Convertibility Into Controlled Substances

No information.

4. General Pharmacology

A. Routes of administration and dosage

Furanyl fentanyl is found as a powder and in liquid solutions, including nasal sprays. In a few cases furanyl fentanyl has been found as tablets and in green herbal materials. It has also been sold as e-liquids for vaping in electronic cigarettes. Routes of administration include oral, intramuscular injection, snorting as a powder, and inhalation (EMCDDA Risk Assessment Report, 2017).

B. Pharmacokinetics

Furanyl fentanyl is metabolized by microsomal oxidation in the liver. Cytochrome CYP3A4 plays a major role. Due to its lipophilicity it is readily absorbed. Recently, Goggin et al (2017) has identified the major metabolites of furanyl fentanyl.

C. Pharmacodynamics

Fentanyl and new derivatives such as furanyl fentanyl have analgesic effect due to their activation of μ-opioid receptors. They also produce respiratory depression that makes them highly risky. Additional pharmacological effects are miosis, sedation, bradycardia, hypothermia, constipation, physical dependence, and changes in mood such as euphoria (EMCDDA-Europol Joint Report 2017).

The binding affinity (Ki) of furanyl fentanyl to opioid receptors was evaluated using an *in vitro* preparation of transfected Chinese hamster ovary cells expressing human δ and κ opioid receptors and rat μ opioid receptors. Furanyl fentanyl showed selectivity for the μ opioid receptor (Ki = 0.0279 ± 0.0080 nM) compared to the δ (Ki = 54 ± 15 nM) and κ (Ki = 59.2 ± 6.4 nM) opioid receptors when [3H]-DAMGO was used as a radioligand. This indicates that furanyl fentanyl is a selective ligand for the μ-opioid receptor. An *in vitro* functional assay found that furanyl fentanyl (EC50 = 2.52 ± 0.46 nM) has μ-opioid receptor agonist activity, similar to morphine (EC50 = 31.0 ± 8.2 nM) and fentanyl (EC50 = 17.9 ± 4.3 nM) (US DEA, 2016).

In mice, furanyl fentanyl has an ED-50 of 0.02 mg/kg in a hot plate analgesia test (Huang et al., 1986).

5. Toxicology

Furanyl fentanyl has been detected in blood samples from 8 fatalities, initially believed to be heroin or other opioid-related drug overdoses. The fatalities occurred in the US between October 2015 and March 2016. However, other drugs were detected in all cases (e.g. U-47700:5, 4-ANPP:5, Quinine:5, morphine:1, tramadol:1, butyrfentanyl:1, delta-9-THC:1) (Moher et al, 2016).

In 281 unintentional overdose fatalities, during January–February 2017, approximately 90% of all decedents tested positive for fentanyl, 48% for acryl fentanyl, 31% for furanyl fentanyl, and 8% for carfentanil in 24 Ohio counties in the US (Daniulaityte et al. 2017).

Furanyl fentanyl (0.34 ng/mL) was detected, along with carfentanil (1.3 ng/mL) and fentanyl (6 ng/mL) in the postmortem blood of a 34-year old male in Florida, US. Morphine and hydromorphone were also detected (Swanson et al, 2017).

The US Drug Enforcement Agency (DEA) has reported that it is currently aware of 128 confirmed fatalities associated with furanyl fentanyl. These fatalities occurred in Illinois (36), Maryland (41), New Jersey (1), North Carolina (49), and Ohio (1) beginning in 2015. However, these fatalities may overlap with those described above. The DEA has suggested that the extent of abuse and mortality associated with this synthetic opioid is likely to be underestimated since it is not included in regular drug screening tests (US DEA 2016).

A cluster of 43 overdose events caused by crack cocaine contaminated with furanyl-fentanyl occurred in British Columbia, Canada (July 2016). 22 patients became unconscious after smoking the cocaine, 40 patients were taken to the emergency department, three of which were put into the intensive care unit (1 died). Furanyl-fentanyl and cocaine were detected in samples collected by the hospital and local police. Reports from first responders, the community, and emergency department staff members indicated that patients required high doses of injectable naloxone, in some cases up to 3.0 mg (usual dose = 0.4 mg) (Klar et al, 2016).

Furanyl fentanyl was also analytically confirmed in 2 fatalities in Sweden, however, other drugs were detected in both cases (e.g. 4-methoxybutyrfentanyl:1). The serum concentrations were 4.4 and 148 ng/mL and in urine 9.2 and 85 ng/mmol creatinine, respectively. Typical clinical features were decreased consciousness, respiratory depression, and miosis. (Helander et al, 2015).

In the EMCDDA-Europol Joint Report 2017, A total of 29 serious adverse events (10 acute intoxications and 19 deaths) associated with furanylfentanyl were reported by Estonia, Germany, Sweden, United Kingdom and Norway.

Of the 10 acute intoxications, 1 case was analytically confirmed and is been described above by Helander et al, 2015. Of the remaining 9 cases, 1 case was probable and 8 were suspected to involve furanyl fentanyl. In 7 of the cases, the clinical features were generally consistent with μ-opioid agonist toxicity including unconsciousness (3 cases) or reduced level of consciousness (2), respiratory arrest or depression (2 cases) and miosis (1 cases) (EMCDDA-Europol Joint Report 2017).

Furanyl fentanyl was analytically confirmed in 19 deaths (Estonia, 4; Germany, 4; Sweden, 9; United Kingdom; 1 Norway; 1) which occurred between November 2015 and October 2016 (EMCDDA-Europol Joint Report 2017). In 12 cases the cause of death was reported as either overdose or intoxication with furanyl fentanyl (5 cases), intoxication with furanyl fentanyl in combination with pregabalin (1 case), overdose of narcotics (2 cases) or intoxication with drugs and narcotics (1 case), or that furany fentanyl in combination with other substances likely played a role in the death (3 cases). The cause of death was either not yet available or not reported for the remaining 7 cases. In 3 cases furanyl fentanyl was the only substance detected. In the remaining 15 cases, other substances were detected including other opioids (such as fentanyl in 7 cases) and other central nervous system (CNS) depressants such as benzodiazepines, ethanol, and gabapentinoids were detected in some of the deaths. In addition, THC, amphetamine, cocaine and MDMA were also detected in some cases (EMCDDA-Europol Joint Report 2017). Misailidi et al (2017) have recently reviewed the fatal cases associated to furanyl fentanyl.

6. Adverse Reactions in Humans

Similar to other μ-opioid agonists, the main life-threatening side effect of furanyl fentanyl is respiratory depression.

7. Dependence Potential

A. Animal Studies

No studies were identified, however, in general μ-opioid receptor agonists have been shown to have dependence potential.

B. Human Studies

No clinical studies were identified.

8. Abuse Potential

A. Animal Studies

No studies were identified that have investigated the abuse potential of furanyl fentanyl in animal models.

B. Human Studies

No clinical studies were identified.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

There are no approved therapeutic applications for furanyl fentanyl.

10. Listing on the WHO Model List of Essential Medicines

Furanyl fentanyl is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

None.

12. Industrial Use

None.

13. Non-Medical Use, Abuse and Dependence

There is increasing use and abuse of furanyl fentanyl. In the EMCDDA-Europol Joint Report (2017), 113 seizures have been reported to the EMCDDA by: Austria (3 seizures), Belgium (3), Cyprus (1), Denmark (1), Estonia (10), Finland (18), Germany (14), Hungary (1), Luxembourg (1), Poland (17), Sweden (38) and the United Kingdom (6).

There has also been an increasing number of fatalities due to the use of furanyl fentanyl in several countries (refer to Section 5).

US DEA National Forensic Laboratory Information System, which collects drug identification results from drug cases submitted to analysis to forensic laboratories, reported an increase in the number drug submissions testing positive for furanyl fentanyl (244 drug submissions from January to July 2016) (CDC, 2016)

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

There are no reports of furanyl fentanyl associated with public health problems such as driving under the influence of drugs (DUIDs). However, it is well established that opioid analgesics, such as fentanyl, can impact the mental and physical ability required to drive and operate machines.

Recently it was reported that samples of crack cocaine were found to contain furanyl fentanyl (Klar et al, 2016). This poses the need of alerting the staff of the emergency departments to evaluate the signs of furanyl fentanyl intoxication in users of cocaine crack in order to use naloxone for their recovery.

In another recent study (Guerrieri et al, 2017) it was reported the presence of pregabalin, in addition to furanyl fentanyl, as a possible contributing factor for the intoxication and death of 5 persons in Sweden.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

Not applicable. Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

Furanyl fentanyl is mainly manufactured illegally in China. Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

Furanyl fentanyl is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

In 2016, furanyl fentanyl was added to the Schedule I Controlled Substances list in USA. It is also illegal in Sweden under national legislation.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None.

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Available at: https://www.regulations.gov/document?D=DEA-2016-0018-0007

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of Furanyl Fentanyl

Please refer to separate Annex 1 document published on ECDD website