



# Critical Review Report: ORTHOFLUOROFENTANYL

Expert Committee on Drug Dependence

Forty-first Meeting

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## Acknowledgements

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## Executive Summary

Receptor binding data show that orthofluorofentanyl binds selectively to the  $\mu$  subtype of opioid receptors with subnanomolar affinity relative to  $\delta$  and  $\kappa$  opioid receptors (DEA-VA, 2017). No pharmacokinetic or pharmacodynamic studies of orthofluorofentanyl are reported in the preclinical or clinical scientific literature. It first appeared in toxicological assays in the U.S. in 2016.

Based primarily on reports of overdoses attributed to orthofluorofentanyl describing naloxone-reversible loss of consciousness, depressed respiration, and miosis, it appears to be a potent mu opioid receptor agonist. As such, its pharmacology and toxic effects are likely to be similar to fentanyl. It currently has no legitimate medical or veterinary uses. Orthofluorofentanyl is being sold as heroin or an adulterant in heroin. Starting in 2016, a number of fatalities have been associated with this substance (1 in Europe and 16 in the U.S.) and it was placed in Schedule 1 by the U.S. on a temporary basis. Because orthofluorofentanyl cross-reacts with standard fentanyl immunoassays, it is possible that the number of deaths associated with it are underreported.

The totality of data currently available on orthofluorofentanyl suggests that it has high abuse potential and poses a serious public health threat.

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### 1. Substance identification

**A. *International Nonproprietary Name (INN)***

Orthofluorofentanyl

**B. *Chemical Abstract Service (CAS) Registry Number***

Not available

**C. *Other Chemical Names***

1-Phenethyl-4-(N-propionyl-2-fluoroanilino)piperidine  
N-(2-fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidiny]-propanamide, HCl

**D. *Trade Names***

None

**E. *Street Names***

None

Other names and code names: ortho-fluorofentanyl, 2-fluorofentanyl, 2-FF, o-FF, o-Fluorofentanyl

**F. *Physical Appearance***

Orthofluorofentanyl is a white crystalline solid (powder).

**G. WHO Review History**

Orthofluorofentanyl has not been reviewed previously by the WHO.

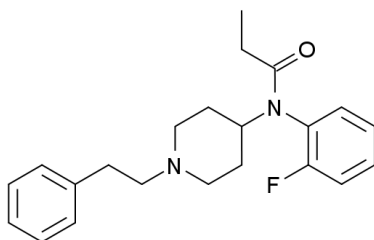
**2. Chemistry**

**A. Chemical Name**

**IUPAC Name:** N-(2-fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide

**CA Index Name:** Not found

**B. Chemical Structure**



**Molecular Formula:** C<sub>22</sub>H<sub>27</sub>FN<sub>2</sub>O

**Molecular Mass:** 354.469

**C. Stereoisomers**

Isomers of orthofluorofentanyl are para- and meta-fluorofentanyl.

**D. Methods and Ease of Illicit Manufacturing**

No reports on the methods and ease of illicit manufacturing orthofluorofentanyl are available in the scientific literature.

**E. Chemical Properties**

Melting point

Not found

Boiling point

Not found

Solubility

Not found

### **F. Identification and Analysis**

Orthofluorofentanyl cannot be differentiated from fentanyl using standard drug screening methods (enzyme-linked immunosorbent assay (ELISA); Guerrieri et al., 2018). Additional tests, such as mass spectrometry, are required. One method of analysis was reported by Swedish investigators: "...three isoforms of fluorofentanyl [ortho-, meta-, and para-] were obtained from Cayman Chemicals, AH Diagnostics, Oslo, Norway. A LC-MSMS (Waters, Acquity UPLC, Xevo TQ-S) method employing a chiral column (CHIROBIOTIC™V, 15 cm × 4.6 mm, 5 μm, Supelco, Bellefonte, PE, USA) that separated the three fluorofentanyl isomers and allowed the quantitation of the different compounds in both serum, blood and urine samples was developed. To 200 μl of calibrators, controls (both in serum, blood and urine matrices) and samples were added internal standard (D5 fentanyl), and the samples were subsequently precipitated with the addition of acetonitrile. The supernatants were transferred to HybridSPE PLus 96-well plates (Supelco) and filtered by positive pressure. Analysis was performed with an isocratic mobile phase consisting of 0.08% formic acid and 0.022% NH<sub>4</sub>OH in methanol. Limit of detection and limit of quantification was ≤0.5 and ≤1.0 ng/mL, respectively, and the calibration curves were linear over the 1–50 ng/mL range with a coefficient of determination >0.99 for all three matrices." (Helland et al., 2017)

### **3. Ease of Convertibility into Controlled Substances**

No reports of conversion of orthofluorofentanyl into other controlled substances were found.

### **4. General Pharmacology**

#### **A. Routes of Administration and Dosage**

Powder containing orthofluorofentanyl has been obtained by regulatory agencies in the U.S. and Sweden. Information from cases submitted for toxicological analyses support the view that orthofluorofentanyl is being used by the intranasal and intravenous routes (Helland et al., 2017; DEA, 2017).

#### **B. Pharmacokinetics**

No controlled pharmacokinetic studies of orthofluorofentanyl have been reported.

#### **C. Pharmacodynamics**

No controlled pharmacodynamic studies of orthofluorofentanyl have been reported.

### **5. Toxicology**

No formal toxicology studies have been performed with orthofluorofentanyl.

### **6. Adverse Reactions in Humans**

No controlled clinical studies have been conducted with orthofluorofentanyl, so adverse reactions in humans are based on reports of fatalities attributed to it. Because orthofluorofentanyl and fentanyl have similar chemical structures, adverse reactions associated with the compound are expected to be similar to fentanyl (e.g., respiratory depression).

Beginning in 2016, 16 confirmed fatalities associated with orthofluorofentanyl were reported in Georgia (1), North Carolina (13), Pennsylvania (1), and Texas (1), based on post-mortem toxicology and medical examiner reports. As noted above, additional confirmatory testing is required to definitively identify orthofluorofentanyl, so the prevalence of this substance in opioid-related emergency room admissions and deaths is most likely underreported (DEA report on orthofluorofentanyl, 2017). An additional report from Sweden described two individuals who experienced non-fatal overdoses associated with orthofluorofentanyl, one of whom was later found deceased in his home with orthofluorofentanyl powder and a paper straw nearby (Helland et al., 2017). The non-fatal overdose symptoms included loss of consciousness, miosis, and low oxygen saturation, all of which responded well to naloxone administration.

## **7. Dependence Potential**

### **A. *Animal Studies***

No preclinical dependence potential studies were found in the published literature.

### **B. *Human Studies***

No clinical dependence potential studies were found in the published scientific literature.

## **8. Abuse Potential**

### **A. *Animal Studies***

No preclinical abuse potential studies were found in the published scientific literature.

### **B. *Human Studies***

No clinical abuse potential studies were found in the published scientific literature.

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

Orthofluorofentanyl is not approved in any country for therapeutic use.

## **10. Listing on the WHO Model List of Essential Medicines**

Orthofluorofentanyl is not included in the WHO Model List of Essential Medicines.

## **11. Marketing Authorizations (as a Medicinal Product)**

Orthofluorofentanyl is not approved in any country as a medicinal product.

## **12. Industrial Use**

Orthofluorofentanyl is available commercially for research and forensic purposes and as an analytical reference standard.

### **13. Non-Medical Use, Abuse and Dependence**

Because of the difficulties associated with positively identifying orthofluorofentanyl in standard assays, the magnitude of misuse and abuse of the drug is likely to be underreported. Given the structural similarity between orthofluorofentanyl and fentanyl, as well as its potent activity at mu opioid receptors, it is expected that orthofluorofentanyl has high potential for non-medical use, abuse, and dependence.

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

Orthofluorofentanyl-related deaths were first reported in the U.S. in 2016: A total of 16 fatalities have been confirmed thus far (DEA report on orthofluorofentanyl, 2017). One death associated with orthofluorofentanyl was reported in Europe (Sweden; Helland et al., 2017).

### **15. Licit Production, Consumption and International Trade**

Orthofluorofentanyl does not appear to have licit medicinal or veterinary use in any country.

### **16. Illicit Manufacture and Traffic and Related Information**

In recent years, the U.S. Drug Enforcement Agency has identified orthofluorofentanyl in STARLiMS, a web-based, commercial laboratory information management system that is used as its laboratory drug evidence data system of record. Starting in 2016, 16 reports containing orthofluorofentanyl were obtained from Georgia (1), North Carolina (13), Pennsylvania (1), and Texas (1).

In addition to STARLiMS, reports of orthofluorofentanyl have appeared in other DEA databases. The National Forensic Laboratory Information System (NFLIS) is a program within the DEA that systematically collects results from drug chemistry analyses conducted by other federal, state and local forensic laboratories across the U.S. These laboratories analyze substances obtained by U.S. law enforcement operations. As of June 20, 2017, NFLIS had 3 reports containing orthofluorofentanyl from state or local forensic laboratories in Virginia in September 2016 (DEA report on orthofluorofentanyl, 2017).

Based on the above evidence, the DEA concluded that the pattern of orthofluorofentanyl abuse parallels that of heroin and prescription opioid analgesics and is used either knowingly or unknowingly.

Limited information is available about trafficking of orthofluorofentanyl.

### **17. Current International Controls and Their Impact**

Orthofluorofentanyl was temporarily placed into Schedule 1 by the DEA on October 26, 2017 [21 CFR Part 1308, Docket No. DEA-473]. The impact of orthofluorofentanyl scheduling is difficult to determine at present.

### **18. Current and Past National Controls**

US: Schedule I (temporary – as of October 26, 2017)

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

None.

## References

Drug Enforcement Administration, Department of Justice. Schedules of Controlled Substances: Temporary Placement of *ortho*-fluorofentanyl, tetrahydrofuranfentanyl, and methoxyacetyl fentanyl in Schedule I. Fed Regist. 2018 Jan 4;83(3):469-72. "Schedules of Controlled Substances: Temporary Placement of Cyclopropyl Fentanyl in Schedule I. Temporary amendment; temporary scheduling order". Federal Register. 82 (206): 49504–49508. October 26, 2017.

Guerrieri D, Kjellqvist F, Kronstrand R, Green H (2018) Validation and cross-reactivity data for fentanyl analogs with the immunoanalysis fentanyl ELISA. J Anal Toxicol 1-7; DOI: 10.1093/jat/bky060

Helland A, Brede WR, Michelsen LS, Gundersen POM, Aarset H, Skjolas JE, Slordal L (2017) Two hospitalizations and one death after exposure to *ortho*-fluorofentanyl. J Anal Toxicol 1-2; DOI: 10.1093/jat/bkx050

*Ortho*-fluorofentanyl, tetrahydrofuranfentanyl, and methoxyacetyl fentanyl: Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling. Drug Enforcement Agency report, July 2017.