

Fentanyl:
Submission to the Expert Advisory Committee
on Drugs

Prepared by the Ministry of Health
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1.0 INTRODUCTION

Fentanyl is being presented to the Expert Advisory Committee on Drugs (the Committee) based on reports indicating that fentanyl abuse is increasing internationally, specifically in North America. As a result, Canada are in the process of scheduling fentanyl precursors. Fentanyl is scheduled in New Zealand as a Class B3 substance under the Misuse of Drugs Act 1975 (MoDA). This issue has been brought to the Committee to generate awareness and discussion around whether the current classification is sufficient at this time, and whether fentanyl precursors be scheduled as is proposed in Canada.

Fentanyl is a synthetic opioid that most commonly causes sedative and analgesic effects. When comparing with other opiates, morphine and pethidine have the closest activity to fentanyl, however fentanyl has a substantially higher potency and is faster acting when compared with both of these substances.

First reported in the 1960s whilst testing for opioid activity, fentanyl was then developed to be used in the medical industry as a pain relief medication. Since then, more analogues of fentanyl have been developed and used for pain relief as well as for illicit purposes.

Abuse of fentanyl and other opioids is becoming an emerging trend around the world. Recent international reports indicate a large increase in the abuse of fentanyl and its analogues, especially in North America. In these countries law enforcement and health data indicate greater availability, increased seizures, and more overdoses from fentanyl than ever before.

Reports suggest that New Zealand has a small opioid using community that generally use diverted and imported morphine and codeine tablets. There is some fentanyl abuse in New Zealand, however it is not commonly abused here at present and its misuse is low compared to other countries.

Fentanyl is currently a Class B3 controlled drug under the Misuse of Drugs Act 1975 (MoDA) in New Zealand. Internationally, fentanyl is a Schedule I substance in the UN Single Convention on Narcotic Drugs 1961, a class A controlled drug in the United Kingdom (UK) Misuse of Drugs Act 1971, a Schedule II substance under the Controlled Substances Act in the United States (US) and a Schedule I controlled drug in Canada under the Controlled Drugs and Substances Act (CDSA). Canada is also moving to schedule the precursor substances for fentanyl. The November 18 2016 Canadian Gazette notice, Regulations Amending the Precursor Control Regulations (Fentanyl Precursors), is attached as Appendix 1. The report on fentanyl use that was considered by Health Canada has been requested and will be provided as soon as possible.

2.0 SUBSTANCE IDENTIFICATION

2.1 Chemical Names/ Trade Names

- Chemical names:

IUPAC name: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide (Pubchem, fentanyl).

Other names: Phentanyl, Fentanil, N-(1-phenethyl-4-piperidinyl)-N-phenylpropionamide, N-(1-phenethyl-4-piperidyl)propionanilide, N-(1-Phenethyl-piperidin-4-yl)-N-phenyl-propionamide, N-(1-phenethylpiperidin-4-yl)-N-phenylpropionamide, N-phenethyl-4-(N-propionylanilino)piperidine, N-phenyl-N-(1-(2-phenylethyl)-4-piperidinyl)propanamide, 1-phenethyl-4-N-propionylanilinopiperidine.

Street names: China White, Drop Dead, Flatline, Lethal Injection, Apache, China Girl, Chinatown, Dance Fever, Great Bear, Poison, Tango and Cash, TNT (Drugbank, fentanyl) (EMCDDA, fentanyl).

Brand names (of medicines):

NZ: Sublimaze, DBL, Sandoz

US: Abstral; Actiq; Duragesic; Fentora; Ionsys; Lazanda; Onsolis [DSC]; Sublimaze; Subsys (Uptodate.com, fentanyl).

2.2 Origin and History

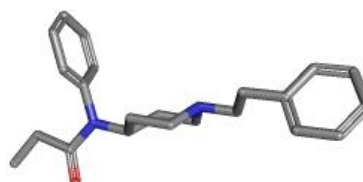
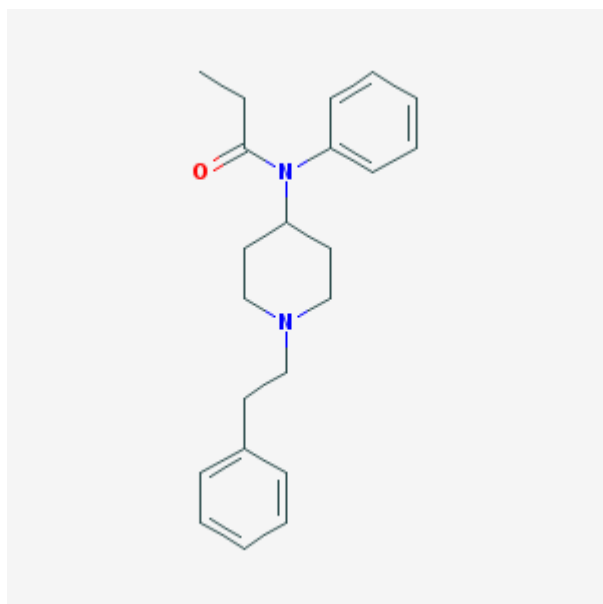
Fentanyl was developed in the 1960s as an analogue of pethidine whilst being tested for opioid activity. It was then used medically as fentanyl citrate (the citric acid salt of fentanyl) as a pain relief medication. Since its early development and use in the medical industry, more fentanyl analogues have been developed and used including sufentanil, alfentanil and remifentanil (News-medical, fentanyl). Sufentanil, alfentanil and remifentanil are all Class B3 controlled drugs under MoDA.

Fentanyl is a narcotic analgesic with a potency at least 80 times that of morphine. Fentanyl and its analogues (alfentanil, sufentanil and remifentanil) are used as anaesthetics and analgesics in medicine. They are subject to international control under the UN Convention on Narcotic Drugs 1961 as are a range of highly potent non-pharmaceutical fentanyl derivatives (such as 3-methylfentanyl) which are synthesised illicitly and sold as 'synthetic heroin', or mixed with heroin (EMCDDA, fentanyl).

The National Drugs Intelligence Bureau (the NDIB) indicate an increase in abuse of fentanyl and its analogues overseas, especially in Canada and the United States. In these countries law enforcement and health data indicates greater availability, increased seizures (fentanyl and its precursors) and more deaths from overdose of fentanyl than ever before (NDIB, September 2016).

There is a concern that these trends will come to New Zealand resulting in a larger opioid dependent population (NDIB, September 2016).

2.3 Chemical Makeup



(Pubchem, fentanyl)

Molecular Formula: $C_{22}H_{28}N_2O$

Molecular Weight: 336.479 g/mol (Pubchem, fentanyl)

Physical form:

Fentanyl and its salts are white granular or crystalline powders. Pharmaceutical formulations occur as solutions of fentanyl citrate for injection, transdermal patches, and transmucosal lozenges. Illicit forms include light yellow powder containing 3-methylfentanyl and occasionally 'paper trips' (thin pieces of cardboard impregnated with fentanyl) (EMCDDA, fentanyl).

Precursors:

- Propionyl chloride
- 1-phenethyl-4-piperidone and its salts
- 4-piperidone and its salts
- norfentanyl and its salts
- 1-phenethylpiperidin-4-ylidenephethylamine and its salts
- N-phenyl-4-piperidinamine and its salts
- N-phenyl-1-(2-phenylethyl)piperidin-4-amine.

Pharmacology:

Like heroin, morphine, and other opioid drugs, fentanyl works by binding to the body's opioid receptors, which are found in areas of the brain that control pain and emotions. When opioid drugs bind to these receptors, they can drive up dopamine levels in the brain's reward areas, producing a state of euphoria and relaxation (drugabuse.gov, fentanyl). A dose of 100 micrograms has the equivalent analgesic activity to 10 milligrams of morphine. Fentanyl works quicker than morphine but for a shorter duration and does not have an emetic (vomiting) effect (NDIB, September 2016).

2.4 Similarity to Other Known Substances

Morphine

Morphine is the principal alkaloid of opium and acts as an opioid receptor agonist which primarily effects the central nervous system and organs containing smooth muscle. Morphine produces many effects, including: analgesia, decreased gastrointestinal motility, respiratory depression, drowsiness, changes in mood and alterations of the endocrine and autonomic nervous systems. Adverse effects include: apnoea, circulatory depression, respiratory arrest, shock and cardiac arrest.

Morphine is indicated for the relief of moderate to severe pain. It is also used as a pre-operative medication and as an analgesic adjunct in general anaesthesia (NZ datasheet: morphine).

Pethidine

Pethidine is a synthetic opioid analgesic which produces a pattern of effects similar to morphine and is indicated for short-term (24-36 hours) relief of moderate to severe pain.

Fentanyl

The analgesic activity of 0.1 mg fentanyl is approximately equivalent to 10 mg of morphine or 75 mg of pethidine. Fentanyl differs from morphine by its short duration of analgesic activity, lack of emetic activity, and minimal hypotensive activity (NZ datasheet: fentanyl).

3.0 REGULATION/ CLASSIFICATION

3.1 Current Regulation/ Classification in New Zealand

Class B3 controlled drug under the Misuse of Drugs Act 1975 and a prescription medicine under the Medicines Regulations 1984.

3.2 International Classification and Experience in Other Jurisdictions

US: Fentanyl is a Schedule II substance under the Controlled Substances Act. The US also controls the precursor, N-phenyl-1-(2-phenylethyl)piperidin-4-amine, as a schedule II controlled substance, the same as fentanyl itself.

UK: Fentanyl is a Class A controlled drug under the UK Misuse of Drugs Act 1971.

Australia: Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

Canada: Fentanyl is a Schedule I substance in the Controlled Drugs and Substances Act (CDSA). Health Canada is in the process of scheduling six precursor substances used to manufacture fentanyl as Class A precursors under Schedule IV of the Controlled Drugs and Substances Act (CDSA). These are:

- Propionyl chloride
- 1-phenethyl-4-piperidone and its salts
- 4-piperidone and its salts
- norfentanyl and its salts
- 1-phenethylpiperidin-4-ylidenephethylamine and its salts

- N-phenyl-4-piperidinamine and its salts.

3.3 UN Classification

Fentanyl has been controlled under Schedule I of the 1961 UN Single Convention on Narcotic Drugs since 1964. Other Fentanyl derivatives which were added to Schedule I include; sufentanil, alfentanil, remifentanil and para-fluorofentanyl. In New Zealand these derivatives are all Class B3 controlled drugs under MoDA. Sufentanil, alfentanil and remifentanil are also prescription medicines under the Medicines Regulations 1984.

4.0 RISK OF HARM IN NEW ZEALAND

4.1 Specific Effects

The action of fentanyl is qualitatively similar to those of morphine and pethidine, that is, analgesia, euphoria, miosis, bradycardia, respiratory depression, bronchoconstriction, muscle rigidity and suppression of cough reflexes. These effects can be reversed by specific opioid antagonists such as naloxone (NZ datasheet: fentanyl).

Fentanyl is contraindicated for:

- children under 2 years of age
- patients with bronchial asthma
- patients susceptible to respiratory depression
- patients who have a head injury or brain tumour (NZ datasheet: fentanyl).

Further warnings and precautions for fentanyl use include:

- drug dependence
- hypoventilation (respiratory depression)
- muscle rigidity
- bradycardia and cardiac arrest
- serotonin syndrome
- use in elderly and debilitated patients
- paediatric use (NZ datasheet: fentanyl).

From 1 January 2012 until now, there have been 57 adverse reaction reports associated with fentanyl in New Zealand, including one death (Medsafe, SMARS).

Adverse reactions seen in greater than 10% of patients using fentanyl are listed below.

Central nervous system: Confusion, dizziness, drowsiness, fatigue, headache, sedation

Endocrine & metabolic: Dehydration

Gastrointestinal: Constipation, nausea, vomiting

Local: Application site erythema (transdermal device)

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea (Uptodate.com, fentanyl).

4.2 Likelihood or Evidence of Abuse

New Zealand has a small opioid using community that generally use diverted and imported morphine and codeine, as well as other opioid pharmaceuticals such as methadone, oxycodone and hydrocodone. The opioid consumer representatives group report a small amount of fentanyl use in New Zealand by people already misusing opioids, however fentanyl is not commonly abused in New Zealand (NDIB, September 2016). Numbers appear to be small due to difficulties obtaining fentanyl through medical diversion, however some do attempt to source it online (NDIB, December 2016).

Fentanyl seizure data:

Year	Quantity Seized	Number of Seizures
2012	0	0
2013	0	0
2014	1 fentanyl patch	1
2015	1.6g acetylfentanyl	1
2016	813 blotter tabs	4
	1 fentanyl patch	1
	10mL fentanyl	1
	6.5g U-47700	1
2017 (Jan-Feb)	0.6g fentanyl powder	1

*Each blotter tab likely contains a small amount of fentanyl.

According to the National Drug Intelligence Bureau's risk assessment on fentanyl, the raw powder is typically exported from China, as well as the precursors to make it. We have seen small amounts of powder come into the country but have not seen any of the precursors here. (NDIB September, 2016)

Findings from an ESR review showed that fentanyl is not widely used in New Zealand, with only 144 cases of fentanyl from more than 24,500 cases investigated in Toxicology from 2002 to 2016. Of those 144 cases, more than 80% of the fentanyl detected was in cases where fentanyl use was for legitimate medical purposes (ESR, 2016).

4.3 Physical or Psychological Dependence

Tolerance and dependence have the potential to develop rapidly after repeated use. Characteristic withdrawal symptoms (sweating, anxiety, diarrhoea, bone pain, abdominal cramps, shivers or 'goose flesh') occur when use is stopped. Serious interactions can occur when fentanyl is mixed with heroin, cocaine, alcohol and other CNS depressants, for example, benzodiazepines (EMCDDA, fentanyl).

4.4 Potential to Cause Death

There has been one reported death in NZ in 2016 where a person applied multiple fentanyl patches at one time. We understand the patches were obtained from another individual (without their permission), to whom they were legitimately prescribed. Internationally, fentanyl and its analogues have contributed to more than 5000 overdose deaths since 2013 (UNODC, fentanyl).

4.5 Therapeutic Value

The principal actions of therapeutic value are analgesia and sedation (NZ datasheet: fentanyl).

Fentanyl is therapeutically indicated for:

- analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance of anaesthesia, and in the immediate post-operative period (recovery room) as the need arises
- use as an opioid analgesic supplement in general and regional anaesthesia;
- administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia
- treatment of chronic pain, in the form of fentanyl patches.

4.6 Risks to Public Health

- Current opioid or psychoactive substance users might switch to fentanyl.
- There is some evidence that other drugs, such as heroin may be laced with fentanyl and sold to unwitting consumers.
- Counterfeit oxycodone, benzodiazepines or other opioid pharmaceuticals purchased over the open and dark web may be adulterated with fentanyl.
- Manufacture of fentanyl from imported precursors could occur, further increasing supply and increasing the chances that individuals will choose to abuse it due to ease of access.
- Customs and Police take all necessary precaution when handling unknown substances but fentanyl poses an additional health and safety risk due to the extremely small amounts required to induce effects.
- Increased use of needles (commonly associated with opioid use) and the associated risks to users and the public such as increased incidences of blood borne infectious agents (eg, HIV and Hepatitis C) from sharing needles. (NDIB, September 2016)

5.0 ANTICIPATED FUTURE TRENDS

Fentanyl is not commonly abused in New Zealand. New Zealand has a relatively small group of opioid users that usually use diverted and imported morphine and codeine pharmaceuticals. There is some fentanyl abuse by opioid users, however it is unlikely that this group is going to increase their misuse of fentanyl due to the low accessibility of the drug. NZ Police and Customs Service seizure data indicates that there have been only small amounts of fentanyl seized in recent years.

Fentanyl precursors have not been seen coming into New Zealand so it is unlikely at this point that fentanyl will be manufactured domestically. This may be due to New Zealand having a smaller market. Bringing precursors into New Zealand would also likely be more complicated than bringing in the finished product, given that it is quite potent, meaning it would be easier to conceal as the finished product since smaller doses are required.

6.0 OTHER RELEVANT INFORMATION

An FDA review has found that the combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system resulted in serious adverse effects, including slowed or difficult breathing and deaths (Uptodate.com, fentanyl).

NDIB extract from last EACD meeting minutes:

Fentanyl is unlikely to be a problem in New Zealand but there is the potential for deaths if it does become an issue. The EACD were asked to consider if the current classification (Class B3) of fentanyl under MoDA is sufficient and the fact that Canada is currently in the process of scheduling all of the precursors for fentanyl, none of which are currently scheduled in New Zealand. The emerging trends aspect of the report looks at very potent synthetic opioids that currently fall under the Psychoactive Substances Act 2013.

7.0 SUMMARY

Fentanyl is a well-known short acting synthetic opioid that is highly potent in comparison with morphine. It has many therapeutic applications, however due to its powerful nature is also commonly abused. Reports in Canada and the United States suggest fentanyl, and its analogues, are being abused more than ever and with its high risk profile and ability to cause death, provides a significant risk to public health. New Zealand does have an opioid using community and fentanyl is present within this community, however, fentanyl does not appear to be commonly abused.

8.0 CLASSIFICATION OPTIONS

Fentanyl option one: Status Quo

Fentanyl remains as a Class B3 controlled drug under MoDA and a prescription medicine under the Medicines Regulations 1984, and all its precursors remain unregulated. Class B3 drugs are commonly used for medical purposes, have lesser dependence potential than B1 and B2 and includes drugs not used in NZ (yet), but have been used internationally.

Class B3 controlled drugs under MoDA do not require Ministerial approval for dealing, importing, exporting, supply and administration of the drug.

All parts of Schedule 2 (Class B's) hold the same maximum punishments, these are; up to 14 years imprisonment for importation, manufacture or supply, and a \$500 fine and up to 3 months in prison, or both, for possession. Penalties for all Class B drugs are the same:

Fentanyl option two: Class B1 or B2

Option two would be to schedule fentanyl as a Class B1 or a Class B2 controlled drug under MoDA.

- Part 1 (B1); Substances that have been generally processed (not natural) and includes opiates with both therapeutic and abuse potential. This option would align with morphine and opium.
- Part 2 (B2); Substances that have less dependence potential than B1 substances, mainly stimulants, and include amphetamines with medical uses.

In contrast to Class B3 controlled drugs, Class B1 and B2 drugs require Ministerial approval for dealing, importing, exporting, supply and administration of the drug.

Fentanyl option three: Class A

Align with the UN Convention, Canada and the UK, and schedule fentanyl as a Class A controlled drug under MoDA.

Class A controlled drugs are severely restricted substances that pose a very high risk of harm to individuals or society. Ministerial approval is required for dealing, importing, exporting, supply and administration of the drug.

Class A substances are generally a mix of hallucinogens, stimulants and depressants such as heroin, LSD, cocaine, PCP and methamphetamine.

The maximum punishments are; life imprisonment for the importation, manufacture or supply (subject to presumption of supply), up to 14 years imprisonment for conspiracy to commit an offence and up to 6 months imprisonment or \$1,000 fine, or both, for possession.

Fentanyl precursor substances option one: Status quo

Fentanyl precursor substances remain unscheduled under MoDA and unregulated overall. This means it will be easy to import precursors and may encourage NZ based manufacture as individuals continue to look for cheap and easy highs.

Fentanyl precursor substances option two: Schedule 4 precursor substances

Include fentanyl precursor substances under Schedule 4 of MoDA. The list of precursors to consider scheduling under MoDA includes all six substances currently proposed to be controlled by Health Canada and the substance already controlled by the US. The list is:

- Propionyl chloride
- 1-phenethyl-4-piperidone and its salts
- 4-piperidone and its salts
- norfentanyl and its salts
- 1-phenethylpiperidin-4-ylidenephethylamine and its salts
- N-phenyl-4-piperidinamine and its salts
- N-phenyl-1-(2-phenylethyl)piperidin-4-amine.

This option does not make it an offence to deal in or be in possession of these substances but gives Customs extra search powers around import and export.

9.0 FUTURE ACTIONS

If the Committee advises that Fentanyl should re-scheduled from a Class B3 to either a Class B2, B1 or A controlled drug and/or its precursor substances should be scheduled, the Secretariat will draft a letter from the Committee to the Associate Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with Industry to ensure impacts on legitimate uses of these substances is reasonable and minimised. If the status quo is kept, no further action is required.

10.0 REFERENCES

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