Flualprazolam:
Report to the Expert Advisory Committee on Drugs

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Contents

1 EXECUTIVE SUMMARY

Flualprazolam is a central nervous system depressant classified as a benzodiazepine in New Zealand. Benzodiazepines are regulated as prescription medicines under the Medicines Act 1981 – unless the substance is explicitly scheduled under the Misuse of Drugs Act 1975.

On 3 November 2020, flualprazolam was reviewed under the Convention on Psychotropic Substances of 1971 by the United Nations Commission on Narcotic Drugs and placed under international control as a Schedule IV substance. As a signatory country, New Zealand is obliged to review the classification of this substance under domestic legislation.

International evidence has shown this substance to be a notable, novel psychoactive substance of abuse. Flualprazolam was first identified as a new benzodiazepine on the European drug market in 2017, and since then has presented itself globally. Domestically it has been seized and detected in samples, with the first notification of its presence in New Zealand from Drug Information and Alerts Aotearoa New Zealand (DIANZ) in 2020. Flualprazolam likely presented on the illicit drug market to circumvent legislation regulating benzodiazepines and benzodiazepine derivatives internationally and domestically. Since its first detection in 2017, many jurisdictions have scheduled flualprazolam as a controlled substance under their domestic legislation.

Flualprazolam has, in a few instances, been detected in drug checking samples from the Institute of Environmental Science and Research (ESR) as well as in toxicology samples. New Zealand Customs Service (Customs) also reported a seizure of flualprazolam tablets in 2021.

Flualprazolam has been associated with sedation, loss of consciousness, memory loss, and disinhibition (effects shared with other benzodiazepines). Due to its potency being greater than other common benzodiazepines, high dosing of flualprazolam can lead to undesirable side effects, and an increased risk of adverse effects. This is especially true when used in conjunction with other central nervous system depressants such as opioids. In many case studies, flualprazolam was commonly present in poly-drug instances. Recreational users have reported strong sedative effects from flualprazolam at low doses. Tolerance and withdrawal from flualprazolam, even after short periods of use, has been noted to present itself suggesting the development of dependence in users.

2 INTRODUCTION

2.1 Purpose

This report provides an overview of flualprazolam which is being presented to the Expert Advisory Committee on Drugs (the Committee) for their consideration and subsequent scheduling recommendations under the Misuse of Drugs Act 1975.

The World Health Organization (WHO) Critical Review Report of flualprazolam from 2019 is provided alongside this paper.

2.2 Substance classification

Flualprazolam is a benzodiazepine, specifically a fluorinated triazolo-benzodiazepine. Benzodiazepines are regulated as prescription medicines under the Medicines Act 1981. Flualprazolam has never been marketed in New Zealand or internationally. There are no accepted therapeutic uses for this substance (WHO 2019).

Flualprazolam was first identified as a new benzodiazepine on the international drug market in 2017. Flualprazolam was notified in the EU Early Warning System in 2018, following the emergence of many designer benzodiazepines being sold and used recreationally in Europe (EMCDDA 2021). Since 2018, there have been an increasing number of flualprazolam seizures reported internationally (Ntoupa et al 2021). As there are no recognised therapeutic uses for flualprazolam, the emergence of this substance on the illicit market likely occurred to circumvent legislation regulating benzodiazepines and benzodiazepine derivatives internationally and within New Zealand (EMCDDA 2021).

2.3 Why is this substance being considered?

In 2020, flualprazolam was scheduled under Schedule IV of the United Nations Convention on Psychotropic Substances of 1971. As New Zealand is a signatory to this convention, flualprazolam must be considered under domestic legislation to meet our international obligations.

3 SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

IUPAC Name:

8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

CAS Number: 28910-91-0

Molecular weight: 326.8 g/mol

Molecular formula: $C_{17}H_{12}ClFN_4$

Appearance: white powder (WHO 2019)

Solubility: soluble in dimethyl sulfoxide and ethanol (Cayman Chemical 2022).

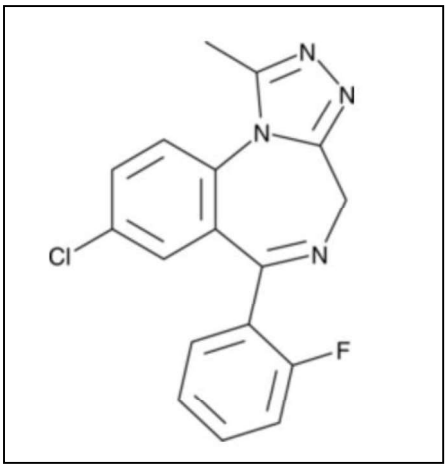


Figure 1: Chemical structure of flualprazolam

3.2 Therapeutic value

Flualprazolam is not used clinically as there are no registered therapeutic uses or products (WHO 2019). It has also never been marketed as a medicinal drug (Ntoupa et al 2021).

3.3 Similarities to other known substances

All benzodiazepines consist of a benzene ring fused to a diazepine ring. The triazolo-benzodiazepine subclass, to which flualprazolam belongs, is distinguished by an additional triazole group fused to the diazepine ring, as shown below in Figure 2.

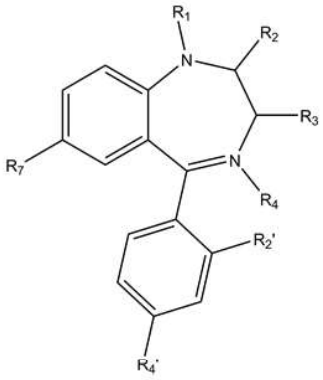
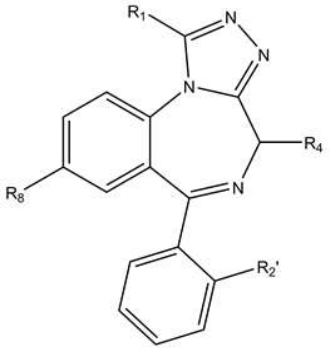
1,4-benzodiazepine	Triazolo-benzodiazepine
	

Figure 2: General structure of benzodiazepines and triazolo-benzodiazepine

Flualprazolam is commonly compared to alprazolam (a Class C5 controlled drug) in relation to its structure, pharmacological properties, and potency, explained below.

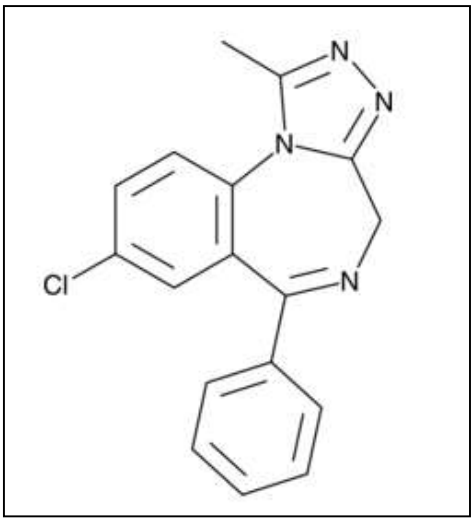


Figure 3: Chemical structure of alprazolam

Structural similarities

Flualprazolam and alprazolam are both triazolo-benzodiazepines. In both structures the diazepine ring is fused to a triazole ring. The only structural difference between these two substances is that flualprazolam has a fluorine atom substituted at the second position of the phenyl ring, whilst alprazolam does not have any substitution on the phenyl ring.

Pharmacological similarities

Although limited pharmacological evidence exists for flualprazolam, it is thought to have similar physiological properties to alprazolam but with much stronger effects. One study found that the substitution of fluorine in the phenyl ring can dramatically enhance activity. Both substances bind at the benzodiazepine site present on some gamma-aminobutyric acid A ($GABA_A$) receptors (ACMD 2020; EMCDDA 2021; Ntoupa et al 2021). Further information on the pharmacology of benzodiazepines is described in section 4.2 of this report.

The duration of action for flualprazolam is longer than that of alprazolam due to the fluorine substitution (Ntoupa et al 2021). Recreational users describe similar effects to alprazolam including strong hypnotic and sedative effects following high dosing (Reddit 2022a).

Similarities in risk of harm

Flualprazolam is known to be significantly more potent by weight than alprazolam (DIANZ 2020b). Recreational users suggest that flualprazolam is 3 to 4 times stronger than alprazolam (Ntoupa et al 2021; Reddit 2020a). In mice, the active dose of flualprazolam is lower than for alprazolam. This provides evidence that flualprazolam is more potent when compared to alprazolam (ACMD 2020; EMCDDA 2021).

3.4 Methods and ease of manufacturing

Flualprazolam was first synthesised and patented in 1976 but was never marketed as a medicinal drug. Since its first synthesis, it has only been noted to be sold on the illicit drug market (Ntoupa et al 2021).

Flualprazolam has been documented to be widely available on the internet (Blumenburg et al 2019). Designer benzodiazepines have been seen to be synthesised in Chinese chemical and pharmaceutical laboratories and shipped internationally as a bulk powder. Once

received at their destination country, they are likely to be processed further into finished products and distributed illicitly (EMCDDA 2021).

Patent US3985052A describes the synthesis of triazolo-benzodiazepines, including flualprazolam. Flualprazolam can be formed by reflux of a solution of 7-chloro-1,3-dihydro-5-(o-fluorophenyl)-2H-1,4-benzodiazepine-2-thione and acetic acid hydrazide in 1-butanol while bubbling nitrogen through the reaction mixture. The solvent is then evaporated in vacuo and the residue treated with water and methylene chloride. The phases are separated, the organic layer dried over anhydrous sodium sulfate, and concentrated to an oil. After titration with ethyl acetate/hexane, flualprazolam is produced by crystallisation from the oil (Google Patents 1976; Ntoupa et al 2021).

4 RISK OF HARM

4.1 Likelihood or evidence of abuse in New Zealand

A NZ Drug Foundation report stated that in 2018, benzodiazepines were the third most frequent drug type, or contributory drug in drug-related deaths (including suicide). In 2017 there were 30 accidental deaths attributed to benzodiazepines. The report also stated that in 2017/2018 woman were more likely to be admitted to hospital for benzodiazepine or opioid overdose (NZ Drug Foundation 2022). This appears to be a different gender pattern compared to presentations of flualprazolam cases in some international case studies where men were more likely to present (Brunetti et al 2021; Kriikku et al 2020). As hospitalisation data does not distinguish between licit and illicit use, the over-representation of women in hospital data may reflect licit use of benzodiazepines as women are more likely to be prescribed benzodiazepines than men (Milani et al 2021; Van der Waals et al 1933).

New Zealand flualprazolam drug laboratory detections

Flualprazolam was first detected by the Institute of Environmental Science and Research (ESR) in September 2020 in New Zealand Police and New Zealand Customs Service (Customs) evidential samples. Since then, there have been 7 detections of flualprazolam by ESR (ESR, personal communications, August 2022).

The 7 detections are as follows:

- in 2 toxicology samples in March 2021. This included one coronial case, and one ‘Unidentified Substances from Emergency Departments’ case from a patient who presented to the emergency department with drug use symptoms
- in 2 Drug Checking samples in 2021
- in 3 New Zealand Police and Customs evidential samples since 2020 (ESR, personal communications, August 2022).

New Zealand flualprazolam seizure data

In 2021, 10 flualprazolam pills were seized by Customs in one incident. According to the National Drug Intelligence Bureau (NDIB) the street value of flualprazolam ranges from $10 to $20 per dose (NDIB, personal communications, July 2022).

4.2 General pharmacology

Flualprazolam is a benzodiazepine and therefore exhibits central nervous system depressive effects (Ntoupa et al 2021). Flualprazolam has been associated with sedation, loss of consciousness, memory loss and disinhibition (Wagmann et al 2020). Generally, benzodiazepines can lead to anxiolytic, anticonvulsant, muscle relaxant, hypnotic and sedative effects (EMCDDA 2021; WHO 2019). Some benzodiazepines can also demonstrate amnesic and euphoric effects (EMCDDA 2019).

Flualprazolam has been noted as a dangerous and potent, novel benzodiazepine which has a relatively short on-set of action and heavy sedative effects (DIANZ 2020a). Recreational users from online forums report strong, sedative effects following high dosing (greater than 1.0 mg), and muscle relaxation and drowsiness at lower doses (0.25 mg) (Reddit 2018).

Whilst there is still only limited data published on flualprazolam, it can be compared to that of other triazolo-benzodiazepines due to its structural similarity. Tests conducted on mice for the sedative, tranquilising and muscle relaxant effects of flualprazolam found it to be more potent than alprazolam (EMCDDA 2021).

Routes of administration and dosage

Oral dosing of flualprazolam has been described as between 0.125mg and 2.0mg (WHO 2019). However, most recreational dosing ranges between 0.125mg and 1.0mg. Undesirable side effects commonly occur at and above these levels (Reddit 2018). Increased tolerance to similar benzodiazepine substances may, in some individuals, lead to examples of higher flualprazolam dosing (Ntoupa et al 2021).

Designer benzodiazepines are commonly presented as powders, tablets, capsules, and in blotter forms. Oral administration has been the most common route of administration for emerging benzodiazepines. However, injecting, vaping and snorting have also been reported (EMCDDA 2021).

Pharmacodynamics

As there is limited evidence on the pharmacodynamics of flualprazolam, it can be compared to that of other triazolo-benzodiazepines. This is due to the presence of the typical benzodiazepine core structure in flualprazolam (Ntoupa et al 2021). It is also thought that flualprazolam acts similarly to alprazolam which has a high affinity for the benzodiazepine site on the $GABA_A$ receptor (WHO 2019).

Benzodiazepines mainly act through binding to the GABA receptor family found in the binding site of benzodiazepine – more specifically to $GABA_A$ receptors which are abundant in the central nervous system (EMCDDA 2021; WHO 2019). The binding site for benzodiazepines is located between the α- and γ-subunit of the GABA receptor (Moosmann and Auwärter 2018).

Benzodiazepines bind as a positive allosteric modulator, leading to an increase in the frequency of GABA-activated-channel-opening thus increasing channel conductance. This results in inhibition of neurotransmission as enhanced chloride permeability at the post-synaptic neuron causes hyperpolarisation and subsequently inhibition (Blumenberg et al 2019; EMCDDA 2021; WHO 2019). This produces the characteristic physiological effects of benzodiazepines.

Pharmacokinetics

Specific information on the pharmacokinetics of flualprazolam is scarce. However, it can be compared to that of other structurally similar triazolo-benzodiazepines, including alprazolam (WHO 2019).

One study determined that flualprazolam's metabolic pathway was similar to that of other triazolo-benzodiazepines. It also showed that cytochrome P450 enzymes and UGT isozymes are involved in the metabolism of this substance (Wagmann et al 2020). Structurally similar triazolo-benzodiazepines are rapidly absorbed and have a high binding affinity to plasma proteins. The fluorine substitution in flualprazolam is thought to increase the potency of flualprazolam due to an increase in binding affinity, when compared to alprazolam (Ntoupa et al 2021). Following administration of flualprazolam, onset of action is reported to be 10 to 30 minutes and the duration of action between 6 to 14 hours. Peak concentrations of alprazolam and triazolam (which are comparable triazolo-benzodiazepines) normally occur within an hour, reflecting rapid absorption, with a high proportion being bound to plasma proteins. It is likely this could be reflective of flualprazolam absorption (WHO 2019).

Metabolism of designer benzodiazepines doesn't tend to differ from traditional benzodiazepines. Therefore, phase I metabolism is mediated through cytochrome P450 enzymes, commonly CYP3A4 (EMCDDA 2021; Ntoupa et al 2021). Phase II metabolism involves glucuronidation and acetylation by uridine 5′-diphospho-glucuronosyltransferase (UGT) and N-acetyltransferase 2 (EMCDDA 2021; Moosmann and Auwärter 2018). The 1,4-triazolo ring prevents the oxidative metabolism of classical benzodiazepines which results in the formation of active metabolites with long elimination half-lives. In healthy adults the average elimination half-life for alprazolam has been documented as 9.5 to 12 hours (WHO 2019).

4.3 Toxicology

Flualprazolam was involved in 778 toxicology cases in 7 countries. The majority of which were reported in 2020 (UNODC 2021). There are limited studies regarding the toxicity of flualprazolam. However, observations show that flualprazolam when used in combination with other central nervous system depressants can lead to serious harm. Fatal overdosing is normally seen in poly-substance cases which makes it difficult to attribute specific harm directly to flualprazolam (Ntoupa et al 2021).

In 2020, a study investigating flualprazolam drug concentrations in post-mortem and impaired driving cases was undertaken. 197 cases were identified with a mean plasma concentration of 20(±63)ng/mL in post-mortem cases and 20(±18)ng/mL in impaired driving cases. In the study, the presence of opioids was detected in 83% of flualprazolam-positive cases. Cases were drawn from 28 American states and one Canadian province (EMCDDA 2021; Papsun et al 2021).

A further study was conducted on rats to determine the correlation between benzodiazepines and opioids in benzodiazepine potentiated opioid-induced respiratory depression. It found that co-administration of a benzodiazepine with heroin induced brain and body hypothermia, and potentiated brain hypoxia. Benzodiazepines prolong the

dangerous effects of opioids which can result in asphyxia causing death (Afzal and Kiyatkin 2019).

4.4 Risk to public health

In 2019, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) early warning system network issued risk communications on flualprazolam highlighting increased availability in Europe. The communication also reported on the flualprazolam related harm being seen in Europe, and the use of flualprazolam in the production of counterfeit tablets of commonly prescribed benzodiazepine medicines, including alprazolam (EMCDDA 2021). Internationally, counterfeit tablets have also been identified in the United States, with the exact appearance and labelling of an alprazolam tablet (Blumenberg et al 2019).

In poly-drug environments with substances such as alcohol, benzodiazepines can cause serious physical and physiological harm. Reportedly, illicit benzodiazepines are used to counteract the effects of opioid withdrawal or to ameliorate the aftereffects of stimulant use. Other pre-clinical evidence has suggested that benzodiazepines can increase the rewarding and reinforcing effects of opioids (EMCDDA 2021; GOV.UK 2020). This may explain why these substances are commonly seen together (Ntoupa et al 2021).

Hospital admissions following ingestion of flualprazolam have commonly occurred in individuals who believed they had consumed alprazolam (Brunetti et al 2021). Patients presented with sedation, verbal impairment and central nervous system depression – symptoms characteristic of high dosing and overdosing of benzodiazepines (Brunetti et al 2021). In 2017/2018, 810 people were discharged from New Zealand hospitals following benzodiazepine overdoses. However, this data has some limitations as it does not distinguish how many of these cases were from non-medical drug use (NZ Drug Foundation 2022).

Flualprazolam is likely to cause disinhibition and sedation that would impair driving (UNODC 2021). Due to the pharmacological action of benzodiazepines, the ability to operate machinery can be greatly impaired under acute influence through changes to reaction times and compromised attention. Sedative effects can also lead to drowsiness and dizziness (EMCDDA 2021). In relation to the increased prevalence of designer benzodiazepines, increased cases of driving impairment and road traffic crashes have been seen. Motor and functional impairment has been observed in cases of driving under the influence of flualprazolam. In Sweden between 2019 and April 2020, flualprazolam was one of the most frequently detected benzodiazepines in driving under the influence of drug cases (Brunetti et al 2021).

Social risks connected to long-term benzodiazepine use can include development of lethargy, lack of motivation, depression and dependence. These can consequently influence an individuals' education, career and relationships (EMCDDA 2021). Reports note flualprazolam and similar substances have been used to sedate and facilitate sexual assault incidents and other violence (Brunetti et al 2021; EMCDDA 2021). Flualprazolam has also reportedly been used as an incapacitating agent for drug-facilitated robbery (Wagmann et al 2020).

In a post-mortem study of Finnish and Swedish accidental deaths and suicides, it was found that most of those deceased were male. The average age for the Swedish cases was 35 years, and for the Finnish cases 23 years (Kriikku et al 2020). In another study looking at case reports on designer benzodiazepines, male users outnumbered female users (Brunetti et al 2021). Whilst there appears to be a gender imbalance in designer benzodiazepine use, no specific research was identified.

In studies undertaken on designer benzodiazepine use and abuse, it is most commonly, young individuals with a previous history of substance abuse and mental illness who use and abuse substances like flualprazolam (Brunetti et al 2021; WHO 2019). An increased prevalence in New Zealand of a substance like flualprazolam could potentially target vulnerable and marginalised populations, who are already more susceptible to poor mental health outcomes, alcohol abuse and other drug use.

4.5 Potential to cause death

Fatal over-dosing of flualprazolam is mostly presented in poly-substance cases. This makes the determination of fatal dose and harm caused from flualprazolam more difficult (Ntoupa et al 2021). Deaths from benzodiazepine toxicity are rare and where it does occur it is generally associated with the concomitant use of benzodiazepines with alcohol, opioids, or other sedatives. Death caused by respiratory depression or aspiration from benzodiazepines used in conjunction with other central nervous system depressants is more common (Blumenburg et al 2019). When flualprazolam is combined with substances such as opioids, it can increase the likelihood of overdose through benzodiazepine potentiated opioid-induced respiratory depression (UNODC 2021).

High doses of benzodiazepines can cause a loss of consciousness and breathing difficulties. As of March 2020, the United Kingdom has reported 12 deaths associated with flualprazolam (GOV.UK 2020). One case study of 33 post-mortem samples found that in 40% of samples, flualprazolam was one of the substances implicated in fatal poisoning. In 2 of these cases flualprazolam was the only substance reported as the cause of death. Both cases contained a blood concentration of 19 and 21ng/g (EMCDDA 2021). In the United States, from August 2019 to February 2020, flualprazolam was detected in 171 post-mortem blood samples. The mean flualprazolam concentration was 20(± 63)ng/mL (EMCDDA 2021).

Due to the higher potency of flualprazolam, a user may be at significantly higher risk of overdose and other adverse effects when counterfeit tablets containing flualprazolam are taken. This is especially true when flualprazolam is used in combination with other central nervous system depressants such as alcohol and opioids.

4.6 Potential for physical or psychological dependence

The dependence potential of flualprazolam is expected to be similar to that of alprazolam and other similar benzodiazepines which are higher potency with a relatively fast onset of action (WHO 2019).

Users have noted that tolerance to flualprazolam builds quickly and following cessation withdrawal symptoms such as insomnia and amnesia have been experienced, likely due to its high potency (EMCDDA 2021; Ntoupa et al 2021; Reddit 2022b). Recreational users have

also noted withdrawal following both prolonged periods of use of flualprazolam, as well as following short high-dose binges (Reddit 2020b; Reddit 2021).

5 CLASSIFICATION

5.1 New Zealand classification and regulation

Flualprazolam is a benzodiazepine, more specifically a triazolo-benzodiazepine and is currently classified as a prescription medicine under the Medicines Act 1981.

5.2 International classification and regulation

Australia

Benzodiazepine derivatives, except when separately specified are listed in Schedule 4 of the Poisons Standard 2022. Flualprazolam is not currently listed as a controlled drug under this legislation (Australian Government 2022).

United Kingdom

In 2020, flualprazolam was scheduled as a Class C controlled drug under the Misuse of Drugs Act 1971 (GOV.UK 2020; legislation.gov.uk 2022).

United States

Flualprazolam is not currently federally regulated as a controlled substance under the Controlled Substances Act 1971. However, some states including Oregon have regulated flualprazolam as a Schedule I Controlled Substance through a benzodiazepine class which includes, but is not limited to, clonazolam and flualprazolam (State of Oregon 2020). Under Schedule I of the Controlled Substances Act, Louisiana, Hawaii and Virginia name flualprazolam as a controlled substance (Louisiana State Legislature 2022; State of Hawaii 2020; Virginia Law 2022).

Canada

'Benzodiazepines, their salts and derivatives' are listed in Schedule IV of the Controlled Substances Act 1996. Flualprazolam is not currently listed as a controlled drug under the legislation (Government of Canada 2022).

Germany

Flualprazolam is scheduled in Annex II of the German Narcotics Drugs Act 1981 (Bundesasamt für Justiz 2022).

Sweden

Flualprazolam is listed under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022).

5.3 UN classification

Flualprazolam was placed under international control at the 63rd United Nations Commission on Narcotic Drugs meeting in 2020. It was scheduled under Schedule IV of the Convention on Psychotropic Substances of 1971 (UNODC 2020).

Substances listed in Schedule IV of the Convention are substances whose liability to abuse constitutes a small but still significant risk to public health which have a therapeutic usefulness from little to great.

6 OTHER RELEVANT INFORMATION

6.1 Anticipated future trends

Due to limited data, it is difficult to anticipate the future trend of flualprazolam use and abuse in New Zealand. However, as demonstrated in international jurisdictions, if this substance was easily accessible as a recreational substance, it is likely that it could cause serious harm in some populations. This is especially true of those already liable to drug use and abuse who also have a history of recreationally using other central nervous system depressants. This could have a serious impact on some marginalised and vulnerable populations within New Zealand.

7 CLASSIFICATION OPTIONS

Option 1 – Maintain status quo

Flualprazolam would remain a prescription medicine under the Medicines Act 1981. The maximum period of supply per prescription would remain at 3 months. By way of comparison substances classified as a Class C controlled drug under the Misuse of Drugs Act 1975 also have a maximum period of supply of 3 months per prescription usually dispensed monthly. Note that flualprazolam is not an approved medicine, has not undergone safety testing, and has no quality assurance. Therefore, prescription is unlikely as any prescription is at the prescriber's own risk.

Anyone caught in possession of a prescription medicine (without a prescription) for personal use faces three months imprisonment and/or a $500 fine. Anyone (other than those exempted under the Medicines Act) convicted of selling or supplying a prescription medicine faces up to six months imprisonment, or a fine not exceeding $20,000.

Option 2 – Schedule as a Class A controlled drug under the Misuse of Drugs Act 1975

Substances posing a very high risk of harm to individuals or society that are highly addictive and liable to abuse or are easily converted into similarly addictive drugs that are liable to abuse.

The regulatory penalties for Class A controlled drugs are listed below in Table 1. For a full breakdown on the controls, please see the EACD guidelines.

Option 3 – Schedule as a Class B controlled drug under the Misuse of Drugs Act 1975

Substances posing a high risk of harm to individuals or society that can be highly addictive and liable to abuse or are easily converted into similarly addictive drugs that are liable to abuse.

The penalties for Schedule 2 (Class B) controlled drugs are listed below in Table 1. For a full breakdown of the differences in control between these parts of Schedule 2, please see the EACD guidelines.

Option 4 – Schedule as a Class C controlled drug under the Misuse of Drugs Act 1975

Substances posing a moderate risk of harm to individuals or society and a moderate to high risk of abuse and dependency or are easily converted into similarly addictive drugs that are liable to abuse.

The penalties for Schedule 3 (Class C) controlled drugs are listed below in Table 1. For a full breakdown of the differences in control between these parts of Schedule 3, please see the EACD guidelines.

Table 1: Comparison of regulatory requirements and penalties under the Misuse of Drugs Act 1975

Class	Requirements	Penalties
A	Ministerial approval required for supplying, administering, prescribing, or granting licences to deal in, import or export Class A controlled drugs – except for cocaine and derivatives. All Class A controlled drugs must be kept in a controlled drugs safe.	Maximum penalty of life imprisonment for the importation, manufacture, or supply (subject to presumption of supply). Up to 14 years imprisonment for conspiracy to commit an offence. Up to 6 months imprisonment or $1,000 fine or both for possession.
B1	Ministerial approval required for supplying, administering, prescribing, or granting licenses to deal in, import or export Class B1 controlled drugs – except for morphine or opium and derivatives. Must be kept in a controlled drugs safe.	All Class B drugs hold the same maximum penalties for offences involving these drugs. Up to 14 years imprisonment for importation, manufacture, or supply (subject to presumption of supply) Up to 10 years imprisonment for conspiracy to commit an offence Up to 3 months imprisonment or $500 fine or both for possession
B2	Ministerial approval required for prescribing, dispensing, and administration. No Ministerial approval required for granting licences to deal in, import or export Class B2 controlled drugs. Must be kept in a controlled drugs safe.	
B3	No Ministerial approval required for supplying, administering, prescribing or granting licenses to deal in, import or export Class B3 controlled drugs. Must be kept in a controlled drugs safe.	
C1	A person who wishes to import, manufacture, and supply or administer a Class C1 controlled drug must apply for a written approval of the Minister for issuance of a licence to do so.	All Class C drugs hold the same maximum penalties for offences involving these drugs. The penalty for anyone caught in possession of a class C controlled drug for personal use without a prescription is the same as that for a

	Class C1 drugs are required to be stored in a safe.	prescription medicine (3 months imprisonment and/or a $500 fine). The penalties for anyone involved in the importation, manufacture and supply of Class C drugs is up to 8 years imprisonment, or, summarily, one year jail and/or a $1,000 fine (similar or slightly harsher than for a prescription medicine). The penalty for conspiracy to commit an offence involving Class C drugs is up to 7 years imprisonment, and up to 3 months imprisonment or a $500 fine or both for possession.
C2-5	A person who wishes to import, manufacture, and supply or administer a Class C2-5 controlled drug must obtain a licence to do so but doesn't need the written approval from the Minister. Class C2-4 drugs are required to be stored in a safe. Class C5 drugs are not required to be stored in a safe.	

8 PRESUMPTION FOR SUPPLY

8.1 Options for presumption of supply

Option 1: Status Quo

Option one is to set no presumption of supply. The default amount of **56 grams** will apply.

This would be approximately **112,000 doses**, assuming that the average dosing was 0.5 mg per day.

This option, being no presumption of supply (and therefore a default of **56 grams**) would align with the presumption of supply set for the other benzodiazepines that are scheduled under the Misuse of Drugs Act 1975.

Option 2: Proposed presumption of supply

Option two is to set a presumption for supply at **12.5 mg** for **25 doses** of flualprazolam, assuming that the average dosing was 0.5 mg per day.

Alternatively, a presumption of supply could be set for **100 doses** of flualprazolam. This would be **50 mg**, assuming that the average dosing was 0.5 mg per day.

9 FUTURE ACTIONS

If the Committee recommends that flualprazolam be scheduled under the Misuse of Drugs Act 1975, the Secretariat will draft a letter from the Committee to the Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with industry to ensure the impact on any legitimate use of flualprazolam is reasonable and minimised. If the status quo is kept, no further action is required.

10 REFERENCES

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